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## AEROSPACE MEDICINE

### MEDICAL RESEARCH IN SPACE FLIGHT

Moscow PRIRODA in Russian No 10, 1977 pp 44-53

[Article by O. G. Gazenko and A. S. Ushakov\*]

[Text] The achievements of domestic science and technology in research on and development of outer space have stimulated the arising of new areas in natural science, to include space biology and medicine. The principal objective of space medicine is to provide medical support to space flight and preserve the health and efficiency of cosmonauts. This is why study of the effects of space factors on the human body, revelation of those which could have an unfavorable influence, and development of the appropriate preventive and protective resources make up the principal part of this new discipline. The objectives of space medicine also include development of medical methods for selecting and training spacecraft crews, and finding the grounds for criteria by which to assess the effectiveness of medical preparation of cosmonauts for flight.

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Arkadiy Sergeyevich Ushakov, doctor of medical sciences, professor, division director in the same institute. Ushakov is studying the problems of metabolism and nutrition in the extreme conditions of space flight.

As a science, space medicine is not very old; it is not even 20 years old yet. We treat 12 April 1962 as its date of birth. The first phase in development of space medicine began with Yuri Gagarin's flight. Flights aboard Vostok spacecraft (1961-1963) proved that man can remain safely in near Earth outer space, and they demonstrated the reliability of methods used to create a normal environment in the spacecraft cabin and the methods for selecting and training cosmonauts.

Growth in the complexity of rocket and space technology has led to creation of Voskhod multiple-crew spacecraft (1964-1965) manned by representatives from different specialties (pilot-cosmonaut, physician, engineer); the medical and physicotchnical research program was broadened as well. Man's walk in outer space was the result, the conclusion of the first phase of space research.

The Vostok and Voskhod flights were followed by a period of regular, systematic flights into outer space. On one hand this promoted successful development of space technology and, in particular, creation of Soyuz spacecraft and Salyut orbiting stations intended for lengthy space expeditions; on the other hand the flights promoted acquisition of preliminary biomedical research data indicating that man's health and efficiency could be preserved in outer space and that flight programs of increasingly greater complexity could be conducted. The first experiments aboard satellites revealed the ways to improve life support systems, medical control, and rescue resources, they defined the tactics to be used in relation to reactions by the cosmonaut's body to the effects of flight factors in different phases of a flight, and they promoted exploration for and development of the ways and means of prevention and active influence during a flight and in the period of readaptation.

Systematic exploration of near Earth outer space by man, using new space technology, began with the flight of Soyuz-3. In addition to technological achievements, manned flights contributed many new things to our understanding of the basic changes occurring in cosmonauts during and after a flight, and they have promoted acquisition of supplementary information required for determination of the ways and methods for preventing the unfavorable influence of space flight conditions.

The medical research program was considerably broadened aboard Soyuz spacecraft and the Salyut orbiting station. As before, however, its main objective was to support flight safety, for which reason special attention was devoted to dynamic control over the health of the crew. During their time in outer space the cosmonauts had to gather information on basic changes occurring in the body, assess the effectiveness of certain resources and methods for preventing the unfavorable effects of weightlessness, determine sensible work-rest schedules for different phases of space flight, and test improved life support systems in their various operating modes.

The flights were conducted in a favorable radiation situation; therefore it is apparent that the physiological reactions of the cosmonauts are not associated with the effects of radiation. The habitation conditions in the spacecraft cabin never strayed beyond the bounds of the prescribed parameters in

all flights. The caloric content of the food of the cosmonauts depended on their energy outlays, being about 2,700 kcal per day.

The four-meal ration of the crews consisted of preserved foods packed in soft tubes, tins, and plastic wrap. Courses in tubes were heated while in flight. Specific features in metabolism in the extreme conditions of space flight, possible changes in appetite, and the individual food preferences of the cosmonauts were taken into account in composing the rations. On the average, each crewmember received 1.6 liters of water in its pure state and about 1.0 liters of water in food per day.

A specially developed complex of hygienic measures maintained the personal hygiene of the cosmonauts.

A work-rest schedule was planned for each flight in accordance with its mission, rest being scheduled as a rule during the time the spacecraft traveled beyond the territory of the Soviet Union. In this connection cosmonauts of most of the lengthy flights lived on a schedule of migrating days, the beginning of which depended on the launch time. Thus the initial daily cycle of the crew of Soyuz-9 was about 9 hours. The flight program foresaw days off, during which the cosmonauts were relieved of practically all work. In contrast to the situation with Vostok and Voskhod, there was no need to use the safety belt system in the cabin of Soyuz, which made it possible to obtain interesting data on the specific features of movement in weightless conditions for the first time.

The flights aboard Soyuz-3 and Soyuz-8 showed that presence in space for several days does not elicit any sort of functional alterations beyond reactions of the human body to extreme effects. At the same time a number of changes occurring in cardiovascular activity, water-salt metabolism, metabolism, in the blood system, in the muscular system, and so on required additional research. This is why a possibility for acquiring biomedical data different from those obtained earlier was foreseen in the preparations for the flight of Soyuz-9. All of the previous flights and research results made it possible to prepare for and conduct this first lengthy flight in the history of cosmonautics, lasting 17 days 17 hours.

The medical control system aboard Soyuz-19 included the recording of electrocardiograms, seismocardiograms, and pneumograms from the cosmonauts both at rest and in the presence of functional loads. A. G. Nikolayev and V. I. Sevast'yanov measured each other's blood pressures as a means of mutual control. The capability for spatial orientation was studied with a Vertikal' device. The cosmonauts reported how they felt in accordance with a prewritten program, using radio and television communication for this purpose.

Specially developed dosed physical exercises helped the cosmonauts to maintain their efficiency and avoid the unfavorable consequences of prolonged weightlessness and hypodynamia.



Table 1. Flights Aboard Soyuz Spacecraft and the Salyut Orbiting Station.

Космический объект (корабль) (1)	Экипаж (2)	Дата запуска (3)	(4) Продолжительность полета, сут	Параметры орбиты (после коррекции) (5)			(8) Начальное время обращения, мин	(10) Индивидуальные дозы радиации	Физиологические методы исследования (11)
				(6) апогей, км	(7) перигей, км	(8) наклон, град			
(12) «Союз-3» (14)	Г. Т. Береговой	26.X.1968	4	225	205	51,4	88,5	85	ЭКГ, пневмограмма, сейсмокардиограмма, научные эксперименты (46)
«Союз-4» (15)	В. А. Шаталов	14.I.1969	3	225	173	51,4	88,25	59	Те же (47)
«Союз-5» (16)	Б. В. Воинов	15.I.1969	3	230	200	51,4	88,7	71	
(17)	А. С. Елисеев							63	
(18)	Е. В. Хрунов							61	Те же
«Союз-6» (19)	Г. С. Шонин	11.X.1969	5	223	186	51,7	88,36		Те же
(20)	В. Н. Кубасов								
«Союз-7» (21)	А. В. Филиппенко	12.X.1969	5	226	207	51,7	88,6	68	Те же
(22)	В. Н. Волков							58	
(23)	В. В. Горбатко							61	
«Союз-8» (15)	В. А. Шаталов	13.X.1969	5	223	205	51,7	88,5	73	Те же
(17)	А. С. Елисеев								
«Союз-9» (24)	А. Г. Николаев	1.VI.1970	18	267	213	51,7	89,05	237	ЭКГ, пневмограмма, сейсмокардиограмма, артериальное давление, исследование работоспособности; научные эксперименты (48)
(25)	В. Н. Севастьянов							403	
«Союз-10» (15)	В. А. Шаталов	23.IV.1971	2	210	193	51,7	88,3	132	ЭКГ, пневмограмма, сейсмокардиограмма; научные эксперименты (46)
(17)	А. С. Елисеев							150	
(26)	Н. Н. Рукавишников							140	
«Союз-11» (27)	Г. Т. Добровольский	6.VI.1971	24	217	185	51,6	88,3	520	ЭКГ, пневмограмма, сейсмокардиограмма, артериальное давление по тахоосциллограмме кинетокардиограмма, сфигмограмма сонной, лучевой и бедренной артерий, флсбограмма, реоэнцефалограмма, функциональные пробы с ОДНТ и велоэргометром; вращательная и статическая пробы; изучение обмена веществ; исследование работоспособности. Научные эксперименты (49)
(13) «Салют» (22)	В. Н. Волков							1233	
(28)	И. И. Пацаев							970	

Table 1. (Continued).

Космический объект (корабль) (1)	Экипаж (2)	Дата запуска (3)	(4) Продолжительность полета, сут	(5) Параметры орбиты (по мере коррекции)				(9) Начальное время обращения, мин	(10) Или продолжительность полета, сут	(11) Физиологические методы исследования
				(6) апогей, км	(7) перигей, км	(8) наклон, град				
«Союз-12» (29) (30) Г. Г. Лазарев	Г. Г. Макаров	27.IX.1973	2	249	194	51,6 88,6		101	50	ЭКГ, пневмограмма, сейсмокардиограмма; научные эксперименты
«Союз-13» (31) (32) Л. И. Климух	В. В. Лебедев	18.XII.1973	5	272	225	51,6 89,22		118	50	Те же и реоэнцефалограмма
«Союз-14» (33) (34) Л. Р. Попович	Ю. П. Артюхин	3.VII.1974	16	277	255	51,6 89,7		265	51	Те же, что и на орбитальной станции «Салют»
«Союз-15» (35) (36) Г. В. Сараф-нов	П. С. Демина	26.VIII.1974	2	275	254	51,6 89,6		--	46	ЭКГ, пневмограмма, сейсмокардиограмма; научные эксперименты
«Союз-16» (21) (26) А. В. Филиппенко	Н. Н. Рукавишников	2.XII.1974	6	223	177	51,8 88,4		88	47	Те же
«Союз-17» (37) (38) А. А. Губарев	Г. М. Гречко	11.I.1974	30	354	293	51,6 90,7		770	51	Те же, что и на орбитальной станции «Салют»
«Союз-18» (31) (25) Л. И. Климух	В. И. Севастьянов	24.V.1975	63	247	193	51,6 88,6		1000	51	Те же, что и на орбитальной станции «Салют»
«Союз-19» (39) (20) А. А. Леонов	В. Н. Кубасов	15.VII.1975	6	225,4	222,7	51,8 88,9		149	46	ЭКГ, пневмограмма, сейсмокардиограмма; научные эксперименты
«Союз-21» (16) (40) Б. В. Волюнов	В. М. Жолотов	8.VII.1976	48	253	293	51,6 88,7		830	51	Те же, что и на орбитальной станции «Салют»
«Союз-22» (41) (42) В. Ф. Быков-ский	В. В. Аксенов	15.IX.1976	7	280	250	65,0 89,6		280	46	ЭКГ, пневмограмма, сейсмокардиограмма; научные эксперименты
«Союз-23» (43) (44) В. Д. Зудов	И. Рождественский	14.X.1976	2	275	243	51,6 89,5			47	Те же
«Союз-24» (23) (45) В. В. Горбатко	Ю. Н. Глазков	7.II.1977	19	281	218	51,6 89,2			51	Те же, что и на орбитальной станции «Салют»

[Key on following page]

Key:

- |   |                         |
|---|-------------------------|
| 1. Space vehicle (craft)  | 22. V. N. Volkov        |
| 2. Crew   | 23. V. V. Gorbatko      |
| 3. Launch date  | 24. A. G. Nikolayev     |
| 4. Length of flight, days   | 25. V. I. Sevast'yanov  |
| 5. Orbit parameters (after correction)  | 26. N. N. Rukavishnikov |
| 6. Apogee, km   | 27. G. T. Dobrovol'skiy |
| 7. Perigee, km  | 28. V. I. Patsayev      |
| 8. Inclination, degrees   | 29. V. G. Lazarev       |
| 9. Initial period of revolution, min  | 30. O. G. Makarov       |
| 10. Individual radiation doses  | 31. P. I. Klimuk        |
| 11. Methods of physiological analysis   | 32. V. V. Lebedev       |
| 12. Soyuz   | 33. P. R. Popovich      |
| 13. Salyut  | 34. Yu. P. Artyukhin    |
| 14. G. T. Beregovoy   | 35. G. V. Sarafanov     |
| 15. V. A. Shatalov  | 36. P. S. Demin         |
| 16. B. V. Volynov   | 37. A. A. Gubarev       |
| 17. A. S. Yeliseyev   | 38. G. M. Grechko       |
| 18. Ye. V. Khrunov  | 39. A. A. Leonov        |
| 19. G. S. Shonin  | 40. V. M. Zholobov      |
| 20. V. N. Kubasov   | 41. V. F. Bykovskiy     |
| 21. A. V. Filipchenko   | 42. V. V. Aksenov       |
| 43. V. D. Zudov   |                         |
| 44. V. I. Rozhdestvenskiy   |                         |
| 45. Yu. N. Glazkov  |                         |
| 46. EKG, pneumogram, seismocardiogram; scientific experiments   |                         |
| 47. As above  |                         |
| 48. EKG, pneumogram, seismogram, arterial pressure, efficiency analysis; scientific experiments   |                         |
| 49. EKG, pneumogram, seismogram, arterial pressure according to a tachoscillogram, kinetocardiogram, sphygmograms of the carotid, radial, and femoral arteries, phlebogram, rheoencephalogram, functional tests with negative pressure on the lower part of the body, and a bicycle ergometer; rotating and (stolitovaya) tests; study of metabolism; efficiency analysis. Scientific experiments |                         |
| 50. As above, and a rheoencephalogram   |                         |
| 51. Same as aboard the Salyut orbiting station  |                         |

Functions of the cardiovascular system, respiration, energy outlays, and the state of the central nervous system and the sense organs were studied during the flight. Efficiency, the level of which was recorded with the assistance of functional tests, was monitored simultaneously.

From the very beginning of weightless conditions, both cosmonauts experienced a rush of blood into the head, which decreased after the first few days and continued to stabilize in the future. The intensity of this sensation depended on the attitude of the body in the cabin. The sharpness of the sensation was noticeably lower when the body was perpendicular to the craft's axis of rotation.

Interesting data were obtained when the cosmonauts attempted motions in the weightless conditions. At the beginning of the flight the cosmonauts experienced difficulty in assessing the amount of muscular effort they were exerting, for which reason their movements were often disproportionate. However, by as early as the third and fourth days of the flight they developed a new motor stereotype and their movements became precise. Thus no disturbances occurred in motor functions, including movement coordination. The crewmembers maintained high efficiency throughout the entire flight.

At the same time, by the end of a hard work day and after completing complex experiments, the cosmonauts began to experience fatigue, which gradually intensified toward the end of the flight. While during the period of adaptation the cosmonauts exhibited a number of signs indicating development of stress reactions, after 3-4 days the physiological indices stabilized at a relatively constant level, increasing somewhat in the last third of the flight. Cardiac rate increased (to 110/min) during performance of physical exercises and after some complex experiments. However, disturbances in cardiac activity were not noted among the cosmonauts throughout the entire course of the expedition, both at rest and in the presence of a physical load. Analysis of their metabolism indicated heightened excretion of potassium, calcium, sulfur, phosphorus, and nitrogen with urine. According to a report from the cosmonauts the sense of thirst was somewhat reduced during the flight, while appetite remained unchanged.

Important data were acquired upon examination of the cosmonauts after the flight. Transition from weightless conditions to Earth's gravity was accompanied by sensations of excessive weight, manifested as a difficulty in maintaining vertical posture, a sense of heaviness of the body, dizziness upon change in posture, and so on. Changes in static measurements and in locomotor functions were noticeable during the first days. The parameters of the shin and thigh decreased, and the density of bones, especially in the lower limbs, declined. After the flight, A. G. Nikolayev lost 2.7 kg while V. I. Sevast'yanov lost 3.9 kg. Significant changes were noted in the muscular system and in circulation. The cosmonauts experienced noticeable strain during active and passive transitions from horizontal position to vertical.

During the period of readaptation, some aspects of metabolism and water-salt metabolism changed (reduction in diuresis, heightened excretion of most electrolytes, and so on), and immunoreactivity was somewhat inhibited. Signs of changes in the bacterial composition of the skin surface, the nasal cavity, and the large intestine were revealed for the first time. Physiological functions returned to normal basically 10-11 days after the flight.

This first lengthy space flight demonstrated that man can remain in weightless conditions for 18 days. The functional transitory changes occurring at this time are purely adaptive in nature. Changes in basic physiological functions are found to be more profound after a flight. This attests to a decline in the body's ability to adapt in these conditions, and it confirms the need for special research and for development of preventive resources facilitating readaptation after lengthy space flights.

The cosmonaut training program was improved and appropriate changes were introduced into the work schedule in space on the basis of the results of the flight of Soyuz-9. The flight of Soyuz-9 was the prelude to future expeditions aboard space vehicles functioning for a long period of time. The tests began with placement of the world's first artificial Earth satellite, the Salyut-1 orbiting station, into orbit.

Table 2. Composition and Calorie Content of the Cosmonaut Diet.

Space-craft	Nutrient Content			Moisture Content, ml	Calorie Content, kcal	Food Assortment
	Proteins, gm	Fats, gm	Carbohydrates, gm			
Soyuz-3	120.9	118.5	267.1	521.5	2,755.0	First courses in aluminum tubes (vegetable shchi, borscht, common soup, rassolnik, etc.). Second courses in tubes (meat puree, poultry puree, marinated mutton, chicken in tomato sauce, etc.); in tins (ham, veal, jellied turkey, zander-al-Neva, meat pate, prepared meat, jellied tongue, etc.). Confectionery (candied fruit, hard chocolate, caramels, cake, fruit sticks, etc.). Fruit and berry juices. Bread (white, rye, Borodinskiy, etc.).  Rations consisting of dehydrated food reconstituted with condensate from atmospheric moisture were used concurrently aboard the Salyut orbiting stations.
Soyuz-4--	110.7	98.2	297.0	672.0	2,586.0	
Soyuz-8						
Soyuz-9	109.7	100.3	339.2	756.3	2,852.0	
Soyuz-10--	126.5	116.7	338.3	697.8	2,992.3	
Soyuz-23						
Soyuz-19	129.2	135.1	289.5	747.6	2,975.7	
Salyut-3--	129.2	135.1	289.5	747.6	2,975.7	
Salyut-5						

Creation of orbiting stations opened up great possibilities for biomedical research in space. These possibilities stemmed chiefly from prolonged presence of man in space in shifts, elimination of a number of unfavorable effects of the habitation conditions through expansion of room, and arising of real possibilities for studying the dynamics behind physiological functions and revealing factors having an effect on man in flight.

The orbiting station was designed in such a way that the parameters of the inhabited environment would be close to comfortable. The amount of motor activity the crew could perform naturally increased due to enlargement of the volume of personal and work compartments; this is why the calorie content of the cosmonaut ration was increased to 3,000 kcal. A broad assortment of personal hygiene resources promoted maintenance of high physical and psychological tone and the efficiency of the cosmonauts.

The results of the 18-day flight of the crew aboard Soyuz-19 served as the grounds for persistent research aimed at seeking the ways and means for preventing the unfavorable effects of weightlessness, and at heightening the capabilities of the body for readaptation. Among them was a complex of dosed physical loads.

These resources were first tested by the crews of Salyut-1 and Salyut-3. Exercising with an integrated trainer and the wearing of weighted suits were positively assessed by the cosmonauts and promoted a better course in the recovery period.

Invaluable data were obtained by the first 24-day expedition aboard Salyut-1. Cosmonauts G. T. Dobrovolskiy, V. N. Volkov, and V. I. Patsayev completed a diverse research program, displaying courage and high responsibility in the performance of their civic and scientific duty. Lengthy expeditions aboard Soyuz-11 and Salyut-1 demonstrated the extreme importance of problems associated with insuring the safety of spacecraft crews.

Analysis of cosmonaut cardiovascular activity at rest and in the presence of functional tests employing dosed physical loads was continued in the 16-day flight of Salyut-3. In this case a tendency toward loss of fitness of the cardiovascular system was revealed with longer flying times. Apparently the changes in sensitivity of the vestibular and statokinetic analyzers noted during the flight and in the time of readaptation were closely associated with changes in circulation. Recovery of physiological functions basically occurred several days after return to Earth.

Highly important results were obtained aboard the Soyuz-17 and Soyuz-18 spacecraft and the Salyut-4 orbiting station. The Soyuz-17 crew, consisting of A. A. Gubarev and G. M. Grechko, which was launched on 11 January 1975, remained in flight for 30 days, completing a broad range of biomedical studies. The longest and most informative flight occurred in summer 1975. The cosmonauts aboard Soyuz-18, P. I. Klimuk and V. I. Sevast'yanov, lived in outer space for 63 days (from 24 May to 26 July 1975). In essence the

experience of all preceding flights was utilized in the preparations for and implementation of the special medical program of this expedition, directed at preventing the unfavorable effects of space flight factors.

An extensive complex of medical studies was conducted in both the first and second expeditions. These studies had the following concurrent objectives: Studying the phenomenology and mechanisms of changes in reactions of the human body in different periods of adaptation to the conditions of lengthy space flight, chiefly weightlessness; assessing the effectiveness of using preventive resources aimed at preventing the unfavorable effects of space flight factors.

Aboard Salyut-4, the cosmonauts had to evaluate an experimental device regenerating water out of condensate from atmospheric moisture and describe the drinking water obtained. This is why the food ration contained experimental samples of dehydrated courses to be reconstituted with water regenerated from condensate. Thus one of the objectives was to evaluate experimental models of some components in the life support systems aboard the space station.

In addition the first attempt at controlling the physiological systems and efficiency of the cosmonauts was made aboard this station. In this case the principle followed was that the cosmonauts were units within the general "crew--spacecraft--ground complex" system.

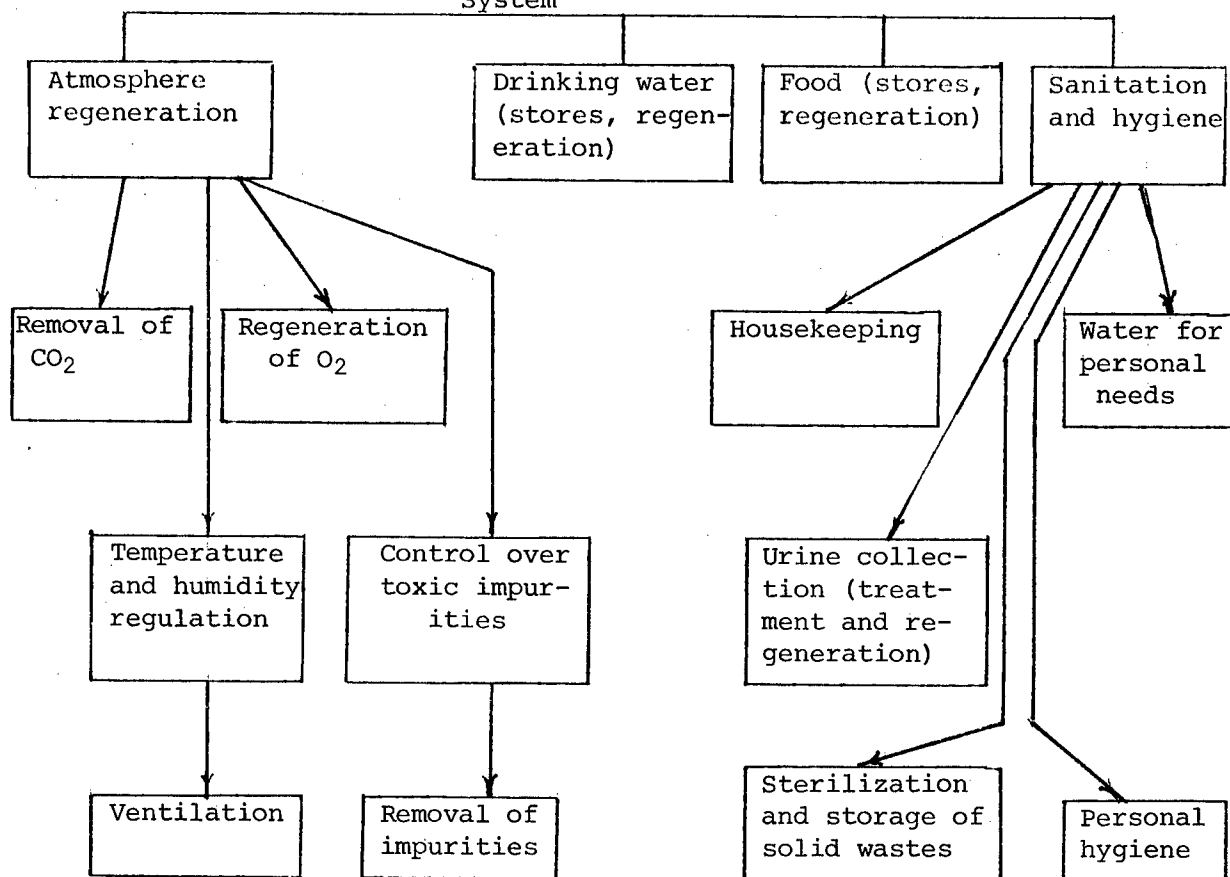
The work-rest schedule foresaw 8 hours of sleep, 2.5 hours of physical exercise, and as much time for eating and personal affairs. About 8 hours were allocated to professional activity, with continuous work not lasting more than 3-4 hours. Days off were given to the crew of the second expedition every 5-6 days in correspondence with the work experience of the first expedition.

The preventive resources included a treadmill, a bicycle ergometer, weighted suits, a pressure suit creating negative pressure in the lower part of the body, and a postflight preventive suit; the food ration contained water-salt and vitamin - amino acid additives. The principal attention was devoted to studying reactions of the cardiovascular system, water-salt metabolism, and metabolism. Research was conducted on the vestibular apparatus, on external respiratory functions, on blood flow to the brain, on microbiological problems, and on a number of other problems.

The initial period of adaptation ended on the 5th day for cosmonauts P. I. Klimuk and V. I. Sevast'yanov. However, adaptation was not complete (because of particular indices) until the 7th-10th days. In the crew's opinion, the experience of former flights was what made adaptation to weightlessness easy. Both cosmonauts reported arisal of light flashes when they closed their eyes, their frequency attaining 5-6 per minute on certain days.

At first the cosmonauts slept for 5-6 hours, and later for 7-8 hours a day. Sleep disturbances were noted in the period of adaptation and in the 4th-5th

# Basic Functions of the Life Support System



weeks of flight, which was apparently associated with migration of onboard days and manifestation of desynchronization.

The efficiency of the crew was generally high throughout the entire flight. Fatigue arising in the first days of the flight was fully compensated for by night sleep.

Electrocardiograms recorded from both cosmonauts were normal for practical purposes, and the changes observed were transitory and functional in nature. Analysis of resting hemodynamics revealed moderate fluctuations in certain indices of arterial pressure for both cosmonauts. The minute blood volume grew in the course of the flight. Indices of the phasal structure of the resting cardiac cycle hardly differed from preflight values or were lower than the latter.

Functional tests employing a physical load on a bicycle ergometer elicited an adequate reaction on the part of the cardiovascular systems of both cosmonauts. However, toward the end of the flight V. I. Sevast'yanov's heart rate somewhat exceeded the preflight value in the presence of a load. A functional test employing negative pressure on the lower part of the body



(ODNT) revealed greater expressiveness of cardiovascular reactions than during the period of ground training, which indicates a decline in orthostatic stability. A water-salt load was administered on the 53d and 62d days of the flight. As a result an improvement in endurance to the ODNT test and higher orthostatic stability were noted.

The perimeters of the thigh and shin of P. I. Klimuk decreased toward the end of the flight. The perimeters of other parts of both of the cosmonauts' bodies remained practically unchanged. Despite the length of the flight, the cosmonauts left the re-entry module on their own and were able to move about actively within the very first hours after touch-down. They were noted to be more susceptible to tiring, and they experienced muscle pains in the first few days. Clinical examination revealed changes on the part of some systems; however, these were functional in nature (decline in body weight, change in coordination, autonomic-vascular lability, changes on the part of the blood system, and so on). The cosmonauts passed functional tests satisfactorily. An analysis of the results of biochemical research showed that the lengthy flight did not cause significant changes in metabolism of the cosmonauts, and that the changes which did occur were adaptive in nature.

Successful completion of the flights aboard the Salyut-4 orbiting station is evidence of significant achievements in space medicine. New training methods were used for the first time in this flight; their results were an important basis for preparations for and conduct of lengthy flights and support of human life in space in the future. This flight was the first to provide us with extensive information on how the cosmonauts felt. We obtained a complete, diverse picture of the work of the entire body.

An extensive program of biomedical research was conducted in weightless conditions by cosmonauts B. V. Volynov and V. M. Zholobov aboard Salyut-5 for 48 days and by cosmonauts V. V. Gorbato and Yu. N. Glazkov for 19 days.

The joint flight of Soyuz (USSR) and Apollo (USA) was a major landmark in the history of space expeditions. The principal objective of the flight of Soyuz and Apollo was to check out the design decisions made and test the technical resources and systems used in search, rendezvous, docking, and mutual transfer of cosmonauts, and in maintaining the required parameters of the artificial gas atmosphere in the inhabited compartments of the spacecraft and the transfer module.

The integrated research program of the experiment flight also foresaw performance of biological experiments. It included research on the effects of weightlessness, cosmic radiation, and the Earth's magnetic field on the growth, development, and genetic structure of various organisms. The biological objects were placed in thermostatically controlled capsules providing the necessary conditions for conducting the research. Three thermostats were installed aboard Soyuz for the "Growth of Microorganisms," "Embryonic Development of Fish," and "Genetic Research" experiments.

The effect of the aggregate of factors of orbital space flight (weightlessness, accelerations, cosmic radiation) on basic biological rhythms was studied in the "Zone-Forming Fungi" experiment.

The "Microbial Exchange" experiment was aimed at revealing the conditions and nature of mutual exchange of microbes between crewmembers. Research of this sort helps us reveal the ways of possible autoinfections as well as infections arising in response to exchange of microbes, which is especially important in sealed cabins of limited space combined with decline in immunoresistance resulting from the effects of space flight factors.

Medical control during the flight as well as clinical-physiological examination of the cosmonauts after touch-down did not reveal any sort of specific features pertaining to the cosmonauts' basic physiological processes in all phases of the flight.

Successful completion of the Soyuz-Apollo experimental flight program was a major step forward in development of international cooperation in development of space--one of the most important directions of modern science and technology.

The experience of manned space flights coupled with scientific analysis of the results of biomedical research attest to the possibility for life and active work by man in outer space, at least for several months when adequately supported.

A new period is beginning in the development of cosmonautics, in which the length of spacecraft flight will reach several months and even years. Perhaps we will now be able to come closer to an understanding of outer space in our research, and even clarify questions concerning the origin of life on our planet. In this case the domain of man's penetration and of active research by him will broaden from near Earth space to the planets of the Solar System.

Biomedical research required in support of flights of the future will be extremely diverse. It will have its grounds in and be defined by all experience acquired in manned space flights.

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METHODOLOGICAL THESES IN BREEDING WHEAT FOR RESISTANCE TO DISEASES IN  
THE STEPPE REGION OF THE UKRAINE AND MOLDAVIA

Leningrad MIKOLOGIYA I FITOPATOLOGIYA in Russian No 4, 1977 pp 328-332

[Article by E. E. Geshele, All-Union Institute of Breeding and Genetics,  
Odessa, submitted 29 Dec 75]

[Text] The problems and methods of wheat breeding for resistance to diseases were described by breeder F. G. Kirichenko and phytopathologist E. E. Geshele at the 6th All-Union Conference on Plant Immunity. Our objective here was to describe the phytopathological characteristics of the region of the southwestern breeding center and outline the breeding process.

The steppe region of the Ukraine and Moldavia is an area of moderate development of rust; however, in some years this disease is quite deleterious, so that breeding for resistance to it is mandatory. Soft wheat is stricken mainly by red leaf rust. Its pathogen, *Puccinia recondita* Rob. ex Desm. f. *tritici*, is represented by virulent biotypes that strike all eight of the international set of differentiator varieties as established by Meyns and Jackson. The use of this set enables us to maintain that there has been prevalence of one strain, 77, for a period of 15 years in the steppe near the Black Sea. However, such a statement is fallacious. This is related to the fact that the international set is already obsolete and does not reflect the changes in pathogen populations that some varieties of wheat from our collection or the set of monogenous strains from Canada can detect. With regard to the population of *P. recondita* f. *tritici* of the southwestern zone, the gene of strain [race]-specific resistance of Lr9 wheat is effective.

We have had information about the race composition of the pathogen since 1961, and we know that there have been frequent changes therein in the southwestern zone, so that specific resistance to one race could not provide for lengthy resistance to disease in the different varieties. This can be seen on the examples of loss of resistance to red rust in the varieties Belotserkovskaya-198, Mironevskaya-808, Aurora and Kavkaz, which were first assigned to the zone as being very resistant to this disease and now have become susceptible. Conversely, the varieties Odesskaya-3 and Bezostaya-1, which presented both race-specific and general resistance when first assigned to the region,

still present moderate resistance, after repeated changes in pathogen strains, to the present composition of the population of pathogen in the southwestern zone. The variety Priboy consists of about 50% biotypes that are immune to the *P. recondita* population at all stages of ontogenesis and about 50% biotypes that present only age-related resistance. In our opinion, such heterogeneity of the variety could result in longer retention of resistance.

Stem rust (the pathogen is *P. graminis* Pers. f. *tritici* Eriks.) develops somewhat later than red rust, and for this reason strikes vernal wheat in particular, as well as winter plantings that are retarded in development. In view of the significant involvement of durum wheat, its resistance to stem rust is one of the principal traits for breeding selection. The winter varieties of bread wheat assigned to this zone present adequate field resistance to stem rust, with the exception of the Priboy variety, but this flaw was taken into consideration in subsequent programs for hybridization and induced mutagenesis.

We have information on the strain composition of *P. graminis* f. *tritici* dating back to 1929. In both the early years of research (1929-1933) and later (1963-1975), there was prevalence of strains 21 and 17. In the last decade there has been more intensive development of strain 34 which strikes the Bezostaya-1 variety of wheat. We attribute the stability of the strains to storage of the pathogen on wild grain plants and small number of uredogenerations in fields of winter wheat, which provides for the same direction of selection in wild grains. Wheat genes *Sr9*, *Sr11*, *Sr13*, *SrTt*, *SrTt* and *Srdv* are effective with respect to strains 21, 17 and 34.

The strain composition of *P. graminis* and *P. recondita* in the southwestern zone was studied in the prewar years (1929-1941) by E. E. Geshele and in the postwar years (1963-1975) by L. T. Babayants, G. G. Anosov (All-Union Institute of Breeding and Genetics), V. V. Shopina (All-Union Institute for the Protection of Plants), A. I. Stanko (Kishinev Agricultural Institute), T. G. Zrazhevskaya (Ukrainian Institute for the Protection of Plants) and N. Ye. Konovalova et al. (All-Union Institute of Phytopathology). The methods and sets of differentiator varieties of international significance are described in the textbook of E. E. Geshele (1971).

E. E. Geshele, L. T. Babayants and G. P. Kozlova spent 3 years (1972-1975) on a comparative study of isolates (uredoclones) of these pathogens from the population, on the basis of using them to infect 3 sets of variety differentiators: international Stackman-Levin and Meyns-Jackson; the one represented by the monogene strains obtained from Canada, the United States and Australia; the one represented by varieties assigned to the region and donors of resistance, which are currently used for hybridization at the All-Union Institute of Breeding and Genetics (VSGI). It has been established that the last two sets are more suitable for breeding work, as well as for the study of the biotype diversity of pathogens.

Yellow rust is encountered less often. In 60 years, there have been 4 epiphytotic outbreaks of this disease in the Black Sea steppe of the Ukraine,

2 of which were quite harmful. There is prevalence of strain 20 biotypes, which differ, according to our studies, from the biotypes of strain 20, which is the ecotype of the nonchernozem region of RSFSR, in that they are more resistant to high temperatures.

Increasing development of powdery mildew is observed in the last decade. This disease is particularly deleterious in areas of irrigated agriculture. The parasite *Erysiphe graminis* DC. f. *tritici* Marchal is represented by many strains, 0, 2, 3, 4, 13, 16, 26, 36, which have been demonstrated by the method involving the use of the European set of differentiator varieties (Nover, 1957). There is prevalence of strains 2 and 4 (analysis made in 1974-1975 by L. T. Babayants, L. A. Dubinina and V. N. Rezvetsov). In breeding new varieties, it is imperative for them to have a combination of general and strain-specific resistance.

The meteorological conditions in the region under discussion are quite favorable for development of wheat and covered smut. The latter inflicts the greatest loss in the case of late planting of winter crops following a dry autumn, when it has to be postponed because of dryness of the soil and late precipitations on outdoor [not in hothouse--"neparovyye"?] precursors.

Investigation of smut parasites revealed that, in the southwestern breeding center zone, they are represented by rather virulent strains (*Ustilago tritici* Jens., strains 12, 13 and 20, species of the genus *Tilletia*, strains 1, 3 and 0, according to the studies of L. A. Dubinina). However, we suggest that breeders work on general (i.e., not strain-specific) resistance, which is quite acceptable for farms that practice seed treatment. Moderate resistance to covered smut makes it possible to omit the use of mercury agents. But in general, seed treatment is necessary, since it is directed not only against different types of smut, but a number of other fungi and bacteria.

Root rot inflicts less damage in our region than in northern Caucasus. In the Black Sea steppe of the Ukraine, there is prevalence of *Fusarium* root rot. *Fusarium* wilt of seeds is encountered only in exceptionally humid years. Penetration of fungi of the genus *Fusarium* from roots to the stalk has been observed (Geshle, Ivashchenko, 1975). While we previously denied the presence in this region of the species *Fusarium graminearum* Schwabe, today we must concede that it can be distributed in the steppe regions of the Ukraine and Moldavia. Helminthosporic root rot (pathogen, *Helminthosporium sativum* Pamm., King et Bakke) is rarely encountered, while the pathogen *Cercospora herpotrichoides* Fron. is observed only in one place (isolated cases).

A phenomenon, which phytopathologists have arbitrarily named "spike defect" is widespread in the region of the southwestern breeding center.\*

It is caused by virosis, root rot, stalk fusariosis and other pathological factors, with subsequent invasion of the spikes and seeds with mildly pathogenic fungi (*Macrosporium*, *Alternaria*, *Cladosporium*, as well as *Fusarium*) and bacteria (Geshele, 1973). It was observed that the "spike defect" is most often observed in wheat varieties that are not sufficiently adapted to the steppe, and for this reason breeders attribute much importance to the selection of breeding numbers that are well-adapted to local conditions. There is intensification of viral diseases of wheat transmitted by aphids and ticks, and mycoplasma diseases the vectors of which are cicadae. In addition to the typical basic bacteriosis induced by *Pseudomonas atrofaciens* Stapp., diverse pathological phenomena are encountered that are induced by other, less pathogenic species and forms of bacteria. The species *Septoria tritici* Rob. et Desm. and *S. nodorum* Berk, which had not previously been known in the steppe regions of the Ukraine and Moldavia, have now advanced there, and this makes it necessary to call the attention of breeders to the need for selection of wheat varieties resistant to these diseases.

On the basis of the reported phytopathological characteristics, tasks have been outlined with respect to breeding wheat in the region of the southwestern breeding center (steppes of the Ukraine and Moldavia). A schedule consisting of four stages has been adopted for the breeding process, in order to augment the yield, improve its quality and resistance in wheat varieties:

First stage: Each breeding program begins with a study of base material: commercial varieties, collections of the All-Union Scientific Research Institute of Plant Growing or other institutions. Then the required purposeful diversity must be created by methods of simple or complex, step-by-step or stage-by-stage hybridization; back-crosses and induced mutagenesis could be used.

Section stage: Selection among the created diversity of plants that are the originators of breeding specimens ["numbers"] against an infectious background with artificial infection by three types of rust and powdery

\*"The spike defects" observed in the southwestern zone differ from the "hollow spike" phenomenon that is well-known to phytopathologists. In the former instance there is a change in color (darker) and shape of spike (very pointed) and development of defective grain. The effect of pathological factors begins even before heading starts. The latter is often inherent in well-developed spikes, in which normal grain development does not occur under the influence of subsequent infection by pathogenic fungi, bacteria and injuries inflicted by insects, ticks, etc. "Empty spikes" or "puny grain" is also induced by adverse weather conditions: excessive humidity--"leakage of grain," and dry winds--"wind burn." In different cases, defective spikes and grain are invaded by the fungi *Alternaria* and *Cladosporium*, which complicate the overall pathological manifestations.

mildew (Geshele, Babayants, 1975). These are the most harmful wheat diseases, against which chemical protection is not planned. Selection for resistance on the basis of one plant (breeding requirement) can be made only with respect to such diseases as rust, powdery mildew and other local diseases. Selection on the basis of one plant that is resistant to smut, root rot and virosis is impossible, since this trait is detected on the basis of testing a certain number of plants, i.e., it is referable to the category of quantitative traits. But when there are already offspring from the forefather of the breeding specimen, selection can be made for resistance to smut, root rot, virosis and other diseases, and at the next stage another evaluation can be made of resistance to rust and powdery mildew.

The third stage of the breeding process for wheat, which is a self-pollinating plant, consists of studying and reproducing the breeding specimens selected at the second stage, with concurrent and constant selection of the best ones. For these purposes, breeding is pursued concurrently against two backgrounds: a) with the first, the specimens are reproduced, their yield is determined and phenological parameters are established; various evaluations are made, including incidence of diseases in the case of spontaneous infection; b) with the second background (or, more precisely, against several backgrounds), isolation of the best varieties according to several parameters for the main testing of a variety is concluded, with artificial infection in the hot house or field using different pathogens.

The fourth is the final stage. Here, the best specimens must be represented in a sufficient number of seeds to sow them for field tests on 100-meter plots repeated 3-4 or more times.

In the main field testing of a variety, the ecological, phytopathological and other evaluations provide the necessary data for holding competitions and selecting the best wheat varieties according to a number of indices used to change a variety. The selected varieties are forwarded for testing to the State Commission for Testing Varieties of Agricultural Crops under the USSR Ministry of Agriculture.

The contest is held according to both productivity and other parameters. In spite of the fact that varieties already bred for resistance to diseases and injuries are submitted for the competitive test, all of the phytopathological evaluations are repeated on a higher methodological level. We call special attention to not only the tests involving artificial infection, but the estimates made in varietal tests on the fields of the breeding institution and different regions that are particularly favorable for the development of disease. Varietal testing in different ecological conditions is a most important factor in demonstrating all their qualities and distinctive features.

In view of the fact that selection primarily for resistance to the main diseases was made at the preceding stages of breeding, at the final stage not only must these parameters be tested using more refined methods, but the varieties must also be tested for secondary diseases. Wheat varieties that

are rather susceptible to secondary diseases, which take up large planting areas, may cause such diseases to become primary in distribution and harmful consequences.

When it is necessary to reject varieties due to susceptibility to smut, root rot and virosis prior to selection of forefathers of breeding specimens, our method of self-rejection, without separating the population into families, should be used (Geshele, 1964). Self-rejection consists of the fact that, against harsh infectious backgrounds, the most susceptible plants do not produce seeds at all or else the seeds are puny, and it is easy to eliminate them from the hybrid population by means of sorting.

Along with the suggestion that breeding specimens be selected against the background of infection with three types of rust and powdery mildew (Geshele, Babayants, 1975), we investigate a number of problems related to mixed infections and correlation between fungi and parasites (Geshele et al., 1975). Possible mixtures of infectious backgrounds at the first stages of the breeding process have also been mentioned in the works of Ye. N. Slyusarenko (1975), L. T. Babayants and L. A. Dubinina (1975).

In the case of step-by-step selection, we used a hard infectious background and selected mainly varieties with strain-specific resistance. In the case of mixed infections, we try to create a moderate infectious background with a pathogen population that is diversified with respect to virulence. General, i.e., nonstrain-specific, resistance should be demonstrated with a moderate infectious background, but with mandatory infection using virulent biotypes of pathogens.

A distinction must be made, not only between types of resistance, but susceptibility, according to the extent of harvest lost due to infection and amount of infectious material generated by the variety for development of epiphytotic outbreaks.

Many susceptible varieties of durum and bread wheat are graded "4" on the Stackman and Levin scale when infected with stem rust, which is the highest mark, i.e., they form normal uredopustules when tested, without manifestation of visible protective reactions; but this does not mean that they are equally susceptible. They may present substantial differences in number of uredopustules formed and sizes, sporulation, duration of incubation period and, mainly, extent of varietal endurance.

The technical procedures for infecting the plants, creating conditions for development of the infectious process, recording immunity and susceptibility used in wheat breeding have been described in our manual (Geshele, 1971).

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## ENVIRONMENTAL AND ECOLOGICAL PROBLEMS

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### PROBLEMS OF RURAL HYGIENE RELATED TO CONVERSION OF LIVESTOCK RAISING TO AN INDUSTRIAL BASIS

Moscow GIGIYENA I SANITARIYA in Russian No 5, 1977 pp 3-8

[Article by K. I. Akulov, A. P. Shitskova, V. A. Savelova, Yu. P. Pal'tsev, V. V. Vlodavets, M. A. Mironenko, I. F. Yarmolik, O. P. Polovtsev, V. I. Chiburayev and N. I. Okladnikov, RSFSR Ministry of Health; Moscow Scientific Research Institute of Hygiene imeni F. F. Erisman; Saratov Scientific Research Institute of Rural Hygiene and Moscow Oblast Sanitary and Epidemiological Station, submitted 3 Jan 76]

[Text] The 25th CPSU Congress approved the planned policy of the Party and government for continued development of specialization and concentration of agricultural production. The decree of the Central Committee CPSU and USSR Council of Ministers issued in 1971 on "Development of production of livestock-raising products on an industrial basis" was instrumental in the rapid construction of cattle and poultry complexes. In recent years, a large number of poultry plants, large complexes for the production of pork, beef, and milk were opened in the vicinity of large cities and industrial centers, and by the end of the Ninth Five-Year Plan, about 1000 livestock complexes were operating in our country. An even broader construction program has been outlined in the Tenth Five-Year Plan, as reflected in the special decree of the Central Committee CPSU issued in 1976, "On continued development of specialization and concentration of agricultural production on the basis of interfarm cooperation and agro-industrial integration," according to which there are plans for the construction of complexes for cattle amounting to 11.5 million head and swine, for 10.5 million head. Concentration, enlargement and, particularly, the changeover to an industrial basis of the animal industry in our country has posed new problems to rural hygiene dealing both with the study of working conditions and health status of those working under the new industrial conditions and investigation of problems related to environmental protection.

The modern complex is a basically new and rather complex industry. The accumulated data indicate that the use of the latest equipment and progressive technology in cattle and poultry complexes has altered radically conditions and nature of work done by animal breeders. Because of the

high degree of mechanization and automation of feed preparation, feed distribution, removal of manure and introduction of a high-power system for ventilation of production areas and air conditioning in large cattle-raising complexes, heavy physical labor is virtually completely eliminated. Working conditions have been significantly improved as a result of setting microclimate standards and lowering to standard levels the amount of dust and specific noxious gases--ammonia, hydrogen sulfide and carbon dioxide--in the air of industrial buildings. At the same time, introduction of modern technology and intensification of labor at cattle-raising complexes may result in appearance of new factors that have a deleterious effect on efficiency and health of service personnel.

For over 2 years studies were conducted on complex hygienic evaluation of the Kuznetsk Swine Breeding Complex, designed to produce 108,000 swine per year. The complex consists of 19 farms, a mixed feed plant, 5 feed-processing departments, as well as installations for water supply and treatment of sewage.

A total of 336 people are employed at this complex, 120 of whom take care of the animals, while the others are involved in repair work, servicing of the water supply and treatment installations, and the boiler room.

Each operator in the feed section services 4200 swine. His job includes feeding the animals and cleaning the premises. They are given liquid feed, or dry feed to fatten nursing sows and piglets (up to 106 days). The distribution of liquid feed is completely automated; to distribute dry feed, manual labor is used in part, along with the mechanized system. As it was determined, 60-80% of the work time is spent by the operator on clean-up, removal of manure by means of hosing it down, but also partly by manual labor (sweeping the floor with scrapers and brooms). The operators work in shifts, on the basis of a 6-day work week and 2 days off; the work day lasts 7 h 42 min, and there is an hour off for lunch. The actual time spent on productive labor is quite high and, according to time studies, constitutes 96% of the work time. Thus, operator work is characterized by a high load during the work day and this, along with rather intensive mental and physical labor, creates the conditions for development of marked fatigue.

A study of the function of ventilating systems at the Kuznetsk complex revealed that the design for the mechanical ventilation system is quite defective with regard to exhaust in relation to influx, and this is the cause of appearance of disorganized streams of air. The hygienic characteristics of the dust factor merits special attention at modern livestock-raising complexes. Most of the dust is referable to dry mixed feed that contains various supplements: protein concentrates, hormones, large doses of vitamins and antibiotics, which could present a health hazard. The concentration of dust in the air of production areas, according to studies made, constitutes 6-10 mg/m<sup>3</sup>, and that of gases is as follows: 4-18 mg/m<sup>3</sup> ammonia, up to 3.5 mg/m<sup>3</sup> hydrogen sulfide and up to 0.3 vol.% carbon dioxide, i.e., it does not exceed the standard. However, in several sectors,

for example the reproduction shop where dry mixed feed is used, a higher concentration of dust has been registered: up to  $17 \text{ mg/m}^3$  with 3.6 to 8.6% free silicon dioxide and up to  $40 \text{ mg/m}^3$  ammonia.

High noise levels of 83-91 dBA have been observed in the feed-processing departments; the sources thereof are the technological equipment, mechanical ventilation, etc., and the animals generate a particularly loud noise when feed is being distributed.

Clinical examination of the workers at the Kuznetsk complex revealed a large number (36%) of individuals with exogenous obesity. In order to determine the causes of such impairment of lipid metabolism in-depth studies must be pursued to make hygienic evaluations of the diet and determine the role of the dust factor, which contains hormones, vitamins and antibiotics. The complaints made by the workers are indicative of functional impairment of the nervous and cardiovascular systems, as well as respiratory organs: headache, general weakness, insomnia, tenderness in the region of the heart, dry and scratchy throat, frequent sore throat. Some workers presented functional changes in the skin of the hands, which could be due to frequent contact with disinfectants and mixed feed.

It is impossible to derive definitive conclusions concerning the deleterious effects of conditions and nature of work on health of employees because of the relatively brief time these individuals have been working at the complex. But there are grounds to classify the livestock breeders working conditions in modern complexes in the category of difficult industries, since there are specific distinctive features involved that could elicit deleterious changes in the functional state of the organism in the case of long work tenure, and they could be involved in development of occupational diseases. For this reason, work in the modern complexes should be equated with labor in industrial enterprises. This will make it possible to raise the question of a need for regular medical supervision of the workers and, in the future, mandatory preliminary and periodic physicals on workers in the main occupations at mechanized livestock-raising complexes.

Questions of environmental protection were found to be even more complicated with regard to designing, building and operating cattle complexes and poultry farms. Animal waste (manure and manure drainage) is the main pollutant of the environment (atmospheric air, water, soil). The system of maintaining livestock and fowl at large farms and farms of the industrial type without the use of litters has resulted in the fact that manure, as a rather valuable organic fertilizer that was previously used in agriculture without restriction, acquired utterly different properties, because of which it is not deemed possible to use it in its unadulterated form in agriculture. The plans implied that long-term storage of manure in its unadulterated state, as was the case before, would cause development of biothermal processes that would lead to destruction of microflora and make it possible to use it as fertilizer. However, it was found that, even in the case of prolonged storage, the conditions do not emerge in litter-free manure for thermophilic and biothermal processes. This is due to its high moisture content

which reaches 70-98%, high levels of ammonia, chlorides (hundreds of mg per liter), as well as other substances and microorganisms.

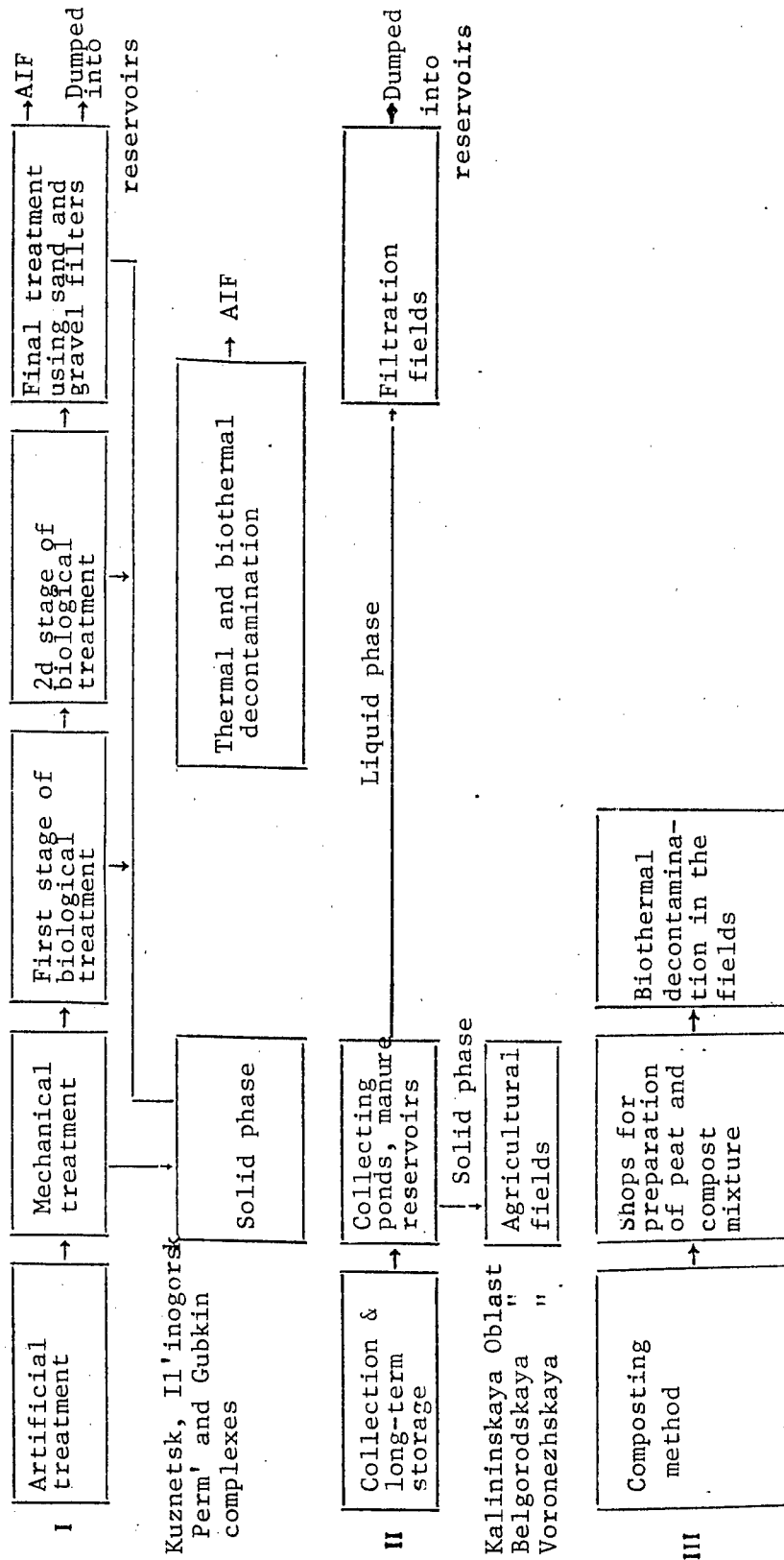
The many investigations pursued by several scientific research institutes (Saratov Scientific Research Institute of Rural Hygiene, Moscow Scientific Research Institute of Hygiene and others), oblast sanitary and epidemiological stations (Moscow, Gor'kovskaya, Leningrad, Belgorodskaya and other oblasts) and All-Union Scientific Research Institute of Veterinary Sanitation have established that, with regard to degree of pollution by organic matter, bacterial contamination, particularly referable to *E. coli* and including those pathogenic to man (different serotypes of salmonella), the waste from livestock complexes and poultry farms (liquid manure and sewage) is considerably more polluted than municipal sewage and waste from enterprises of the food industry. It constitutes a rather favorable medium as well for preserving viability of the pathogens of a number of infectious diseases.

Application of litter-free manure and livestock sewage consisting of cattle and swine excrements in the soil caused intensive bacterial contamination thereof. It was found that pathogenic bacteria, including salmonella, remained intact for 4-5 months in the soil of agricultural irrigation fields (AIF). Cultivated crops (vicia and oat mixture, corn, perennial grass and wheat) that are grown on fields irrigated with livestock waste were contaminated by pathogenic bacterial serotypes in almost all cases. It was also found that, under appropriate conditions, when waste is added to the soil by the sprinkler method from the air, helminth eggs also spread over a distance of up to 400 m.

The distinctions of chemical composition and high concentration of organic substances, which are in a suspended and colloid state, make it impossible to use the ordinary technological systems and installations used for municipal sewage to treat manure sewage. Treatment and decontamination of manure sewage are now being performed primarily by three systems.

Hygienic evaluation of the operation of various systems for treatment of waste at major livestock complexes that began to operate in 1971-1975 revealed that a significant part of the existing systems does not meet the hygienic requirements, either with regard to effectiveness of treatment, or conditions under which sewage is dumped into reservoirs, because of the distinctive features of livestock waste, designing or operating flaws.

It has been established that the problems of decontamination of raw sediments and dehydration of silt have not yet been resolved in the technological system of artificial biological treatment (see Figure, I). However, the knowhow gained by sanitation and hygiene institutions in checking the operation of various systems of gathering, storing, transporting, decontaminating and utilizing manure and sewage at livestock industry complexes and farms has made it possible to develop 13 model designs that were approved by the USSR Ministry of Health in 1976.



Novyy Svet swine complex in Leningrad Oblast

Chart of systems used at the present time for treatment of sewage at large livestock complexes

The livestock complexes not only pollute surface reservoirs, subterranean water and soil, they are also the source of pollution of atmospheric air in inhabited centers. According to the data of the Siberian Scientific Research Institute of Agricultural Construction [Sel'khozstroy], a swine complex with a capability of 108,000 head per year, dumps 1.5 billion microorganisms, 159 kg ammonia, 14.5 kg hydrogen sulfide and 25.9 kg dust from feed into the atmosphere per hour. In areas where there are large farms, there are high concentrations of ammonia, unpleasant odor and bacterial contamination of the air. Irrigation of fields with sewage that has not been adequately treated, from swine complexes, also fails to assure good sanitation in housing and prompts justifiable complaints by the public about air pollution.

Analysis of the facts made it possible to establish the patterns of spread of atmospheric air pollution as related to the types and sizes of the complexes and to approach the solution to problems of where to locate the complexes and develop differentiated standards concerning protective sanitary belts. Thus, at the present time, a sanitary protection zone of 2.5 km has been set as the standard for poultry complexes of the pavilion and mixed types, up to 3 km for cattle complexes with a 10,000 head capacity, 5 km for swine complexes with 108,000 head and 10-15 km or more when the complexes are enlarged to 216,000 and 432,000 head. The considerable size of these zones is necessary due to the high yield from the sources of pollution, as well as lack of systems in the complexes for treatment of waste dumped in the atmosphere and methods of treating waste that would rule out pollution of atmospheric air.

Thus, a summary of the data of sanitary and epidemiological stations and the results of specially conducted hygienic studies at the Moscow Scientific Research Institute of Hygiene and other institutions justifies the classification of large livestock complexes among the major sources of environmental pollution.

For this reason, we are faced with acute problems of early hygienic evaluation of plans and construction, and especially the technical material and equipment of complexes and poultry farms. The following important questions must also be borne in mind: a) location of production buildings and treatment installations in relation to the developed zone; b) availability of the required land areas for utilization of animal industry waste; c) scientifically substantiated standards with respect to sewage loads per hectare of land, depending on soil-climate and hydrogeological conditions; d) transportation of the liquid waste fraction (tank trucks or pipes). The types of sprinkler installations for irrigation of cultivated land have been studied inadequately, yet they require the most attentive attitude and comprehensive hygienic evaluation. Of course, prevention of bacterial and chemical pollution of the air basin, water resources and soil depends on prompt implementation of scientifically substantiated hygienic recommendations.

The industrial type of livestock raising, which has been widely developed in our country, requires development, within the next few years, of basically new scientific and technical projects, directed toward protection of the

environment (water, soil and atmospheric air of rural populated centers), which should aim toward developing waste-free and sewage-free technological systems that would assure complete utilization of waste. For this reason, at the present stage, it is imperative to widen comprehensive research of hygienists in collaboration with specialists from scientific research institutes of the Ministry of Agriculture, architects, technologists, builders and livestock breeders.

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## GENETICS

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### FORUM OF GENETICISTS AND BREEDERS

Moscow VESTNIK SEL'SKOKHOZYAYSTVENNOY NAUKI in Russian No 10, 1977 pp 138-141

[Excerpts from article by N. M. Grigor'yeva]

[Text] In a paper entitled "Genetics and Social Problems," Academician N. P. DUBININ reported that genetics, which deals with phenomena of heredity and variability, is the central science of all modern teaching on life, and the solution of the major practical problems involves the use of advances therein. The production of an abundance of products and raw material depends largely on advances in genetics and use thereof in agriculture and the microbiological industry.

Breeding has undergone significant development in our country. General knowledge of the laws of heredity and variability served the needs of breeding. N. I. Vavilov was the leader of this scientific trend; he is the one who developed the ecological and geographic principles of breeding and the law of homologous series of hereditary variability. The collection of worldwide plant resources gathered at the All-Union Scientific Research Institute of Plant Growing [VIR] had a profound influence on Soviet breeding.

The speaker then listed the main procedures and methods used in Soviet breeding of agricultural plants. Problems of remote hybridization were and are being resolved in the work of I. V. Michurin, N. V. Tsitsin, G. D. Karpechenko and others. Thanks to the advances in general genetics, much has been achieved with respect to development of remarkable varieties, as indicated by the works of A. P. Shekhurdin, V. S. Pustovoyt, P. P. Luk'yanenko, V. N. Remeslo, F. G. Kirichenko, P. F. Garkavyy and A. L. Mazlumov, dealing with wheat, sunflowers, barley, sugar beets, corn and other crops.

The use of special methodology in genetics had a great influence on the success of breeding (the work of M. I. Khazhinov on controlled heterosis in corn; V. A. Panin, A. N. Lutkov and V. P. Zosimovich, on polyploidy of sugar beets; G. A. Nadson, A. A. Sapegin, L. N. Delone and I. A. Rapoport on the use of radiation and chemical mutagens in breeding microorganisms and plants; V. A. Strunnikov on structural and other mutations in silkworm breeding, and others).

Induction of mutations not only makes it possible to improve various features, but to develop new properties. The radiation mutant of P. K. Shkvarnikov and I. V. Chernyy served as the basis for developing the Novosibirskaya 67 variety of spring wheat. The alkaloid-free lupine of V. I. Golovchenko resulted in a new strain of this plant. The task has been formulated of developing cold-resistance genes in winter wheat. A. F. Shulyndin, who used amphidiploids of wheat and rye hybrids, developed some promising forms of a new grain plant, triticale. N. A. Lebedeva, who combined experimental polyploidy with remote hybridization, developed a new method of breeding potatoes.

In several of these works, we are already finding elements of the third stage of breeding, which is characterized by the fact that the logically designed models of varieties, strains and breeds created by the purposeful use of a set of genetic and breeding techniques. Development of special genetics, biochemistry and physiology of each of the objects involved in the breeding is of paramount importance to the performance of these tasks.

N. P. Dubinin observed that breeders are confronted with tasks that exceed everything that has already been done in this field in the entire history of agriculture and animal breeding. The productivity per hectare of cultivated land, meadows, pastures, truck gardens and forests must be increased 3-4-fold, and for this there must be implementation of purposeful genetic and breeding plans, each of which should solve the problem on a regional and national scale, in accordance with the plans for socialist countries and, in some cases, on a worldwide scale. Of great importance are the quality of agricultural production, yield and upgrading such traits as immunity to diseases, absence of lodging and winter hardiness in wheat, rye, rice and other grain crops, resistance to wilt and leaf shedding in cotton, increased sugar yield per hectare of beets, resistance to diseases in potatoes, multiple cobs in corn, early ripening and the quality of pulp in trees, etc.

N. P. Dubinin expressed the hope that in the near future genetic breeding will experience the transforming effect of genetic engineering, which controls heredity and will transfer the development of new varieties of plants and breeds of animals to the level of subcellular and molecular structures. There is a possibility of obtaining recombinant molecules of DNA and introducing them into a selected cell. Thus, experimental investigation is in progress of the possibility of transferring the genes of fixation of nitrogen of air from bacteria to the cells of higher plants.

The group of studies dealing with genetics and breeding, directed toward increasing the volume and improving the quality of food and raw material, is of importance to the solution of basic social problems. Genetic breeding is the cheapest method of intensifying agriculture and the microbiological industry. Backed up by the advantages of socialist, genetic breeding of plants will, by developing highly productive varieties with the set of required useful traits, eliminate the need agriculture is experiencing of increasing significantly power used per production unit and expenses of the fertilizer industry and chemical protection agents, since all this will provide an abundance of cheap products and raw material.

The speaker then stated that mankind is experiencing the consequences of the scientific and technological revolution: many chemical and physical agents are getting into the biosphere; they penetrate into human cells and injure the DNA molecules. Discovery of the danger of environmental agents is a great achievement of genetics, while prediction of an increase in genetic lesions and control thereof is an enormous task that this discipline faces.

Substantiation of the teaching on man as a biosocial being is a major achievement of genetics. In the opinion of N. P. Dubinin, development of the personality is a dynamic process, in which social conditions, based on the influence of the genetic program of man, play a leading role.

By virtue of the advances of genetics, modern philosophical materialism has obtained proof of the material nature of all of the principal phenomena of life. Interaction of proteins, nucleic acids and exogenous energy constitutes the essence of phenomena of life.

N. P. Dubinin concluded his speech with the statement that the next decades of development of Soviet science will be marked with enormous advances in genetics, which is called upon to provide an abundance of food resources, health and longevity of man, harmonious development of his capabilities, development of the required environment of man. All this will aid in implementing the grand ideals of communism concerning man as the goal of society.

\* \* \*

Academician D. K. BELYAYEV, in a paper dealing with some problems of genetics of stress, arrived at the conclusion, on the basis of the results of many years of research on silver foxes and other animals, that stress is of great form-producing significance, and he discussed the possibility of selection of stress-resistant specimens. But the extent to which stress reactions in animals are genetically determined is still unclear. This is a basic question, and the very concept of stress must be broadened to answer it.

In addition to the plenary sessions, there were 15 symposiums at the congress dealing with the following topics: genetics of development; population and evolutionary genetics; problems of mutagenesis; patterns of organization and function of the genetic system; recombination and genetics of plasmids; genetics of phages; genetic bases of breeding microorganisms; genetic bases of plant selection (biochemical genetics, mutagenesis and genetics of chloroplasts); genetic bases of plant breeding (genetics of systems of reproduction and polygene traits); genetic bases of plant breeding (special genetics and cytogenetics of plants); plant breeding; breeding wheat and triticale; genetics and breeding of animals; medical genetics and human genetics; problems pertaining to the teaching of genetics at VUZ, and there were 19 section meetings: on genetics of development; population genetics; the mutation process; structure and function of chromosomes; genetics of behavior; molecular genetics of prokaryotes; molecular genetics of eukaryotes; genetics and breeding of microorganisms; special genetics of agricultural plants; remote hybridization and cytogenetics of plants; breeding of grain crops; breeding cereal, feed and technical crops; breeding fruit, vegetables and potatoes; genetics and breeding

of trees; genetic and breeding research on cattle, goats and sheep; genetics and breeding of small farm and laboratory animals; human genetics; human cytogenetics and genetics of somatic cells; hereditary diseases.

We shall discuss only some of the papers and speeches delivered or made at the congress, which are related to agriculture. The program of the symposiums devoted special attention to the genetic bases of plant breeding.

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FORMATION AND DEVELOPMENT OF ANTIBIOTIC SCIENCE AND PRODUCTION IN THE USSR

Moscow ANTIBIOTIKI in Russian No 10, 1977 pp 878-892

[Article by S. M. Navashin, M. M. Levitov, Ye. K. Berezina, Ye. S. Bylinkina, S. A. Zhukovskaya, Ye. M. Savitskaya, N. V. Orlova, Yu. O. Sazykin, and Yu. E. Bartoshevich, All-Union Scientific Research Institute of Antibiotics, Moscow]

[Text] The 60th anniversary of October--a historic date in our country's history--coincides with an important landmark in the development of domestic antibiotic science and production. Thirty years ago, the first institute on this problem--the All-Union Scientific Research Institute of Antibiotics (VNIIA)--was organized, and antibiotic plants were created.

Today, domestic antibiotic industry holds second place in the world in relation to production volume, and it is producing practically all of the most important antibiotics of various groups. The overall potential of microbiological synthesis is growing in the national economies of the socialist countries. Not only have Soviet scientists and plant workers created an antibiotic industry in the USSR within a short time; they are also providing scientific-technical assistance to socialist and developing countries.

I

The history of the formation and development of antibiotic science and industry in our country is interesting and instructive from various points of view. A very specific production sector was created within a short time through the joint work of scientific and plant collectives. This sector required new specialties in general, technical, and medical microbiology. Without these new fields in microbiology, it would have been impossible to acquire, study, and introduce antibiotics into practice. The integrated nature of the new science and the need for mandatory participation of representatives of many specialties besides microbiology--chemistry, biochemistry, chemotherapy, pharmacology, pharmaceuticals, technology, and so on--in its development have brought on the need for creating large scientific collectives united into a single whole. The All-Union Scientific Research Institute on Penicillin and Other Antibiotics (presently the VNIIA), which began its activities in 1947, became the center for work in antibiotics. Z. V. Yermol'yeva made a major contribution to organizing the institute. The institute

enjoyed broad support from the USSR Academy of Sciences, the USSR Academy of Medical Sciences, the USSR Ministry of Public Health, university departments, and institutions of higher education during its creation and in all subsequent stages of its formation and development. The Antibiotics Commission headed by L. A. Orbeli and A. I. Oparin functioned successfully in the 1950's under the USSR Academy of Sciences, playing an important role in organizing this new sector of science and production and in coordinating research. It would be sufficient here to mention the names of scientists belonging to the USSR Academy of Sciences and to the academies of sciences of the union republics who had made a significant contribution to development of the antibiotic problem. There was fundamental significance to development of domestic antibiotic science in research by N. A. Krasil'nikov on classification and taxonomy of soil microorganisms, by V. N. Shaposhnikov, A. A. Imshenetskiy, and N. D. Iyerusalimskiy on antibiotic physiology and biosynthesis, and by Ye. N. Mishustin on the basic laws governing soil ecosystems.

Antibiotic chemistry enjoyed development in our country in the fundamental works of M. M. Shemyakin, Yu. A. Ovchinnikov, M. N. Kolosov, A. S. Khokhlov, and L. D. Vergel'son. Molecular mechanisms behind antibiotic actions were studied by Yu. A. Ovchinnikov, A. S. Spirin, A. Ye. Braunshteyn, V. A. Engelgardt, and A. A. Bayev. A role of no small importance in development of antibiotic science was played by I. A. Rapoport's research on chemical mutagenesis and Ya. I. Rautenshteyn's research on actinophagy.

Among achievements which have received worldwide recognition, we should note complete synthesis of tetracycline (M. M. Shemyakin, M. N. Kolosov) and clarification of the structure and conformation of cyclic depsipeptides as membrane-active complexones (Yu. A. Ovchinnikov).

## II

Valuable material on the distribution, biology, and classification of ray fungi was accumulated before industrial antibiotic production began in the USSR. In those days, this research was carried on basically in a division of the USSR Academy of Sciences Institute of Microbiology headed by N. A. Krasil'nikov. Krasil'nikov's school made a substantial contribution to development of the teaching on actinomycetes--antibiotic producers. Lengthy, diverse research on actinomycetes resulted in publication of "Opredelitel' bakteriy i aktinomitssetov" (Guide to the Bacteria and Actinomycetes) and the monograph "Luchistyye gribki" (Ray Fungi), which have become standard references for specialists conducting research on the biology and classification of actinomycetes.

Expansion of antibiotic production through the addition of new compounds obtained through microbiological synthesis and the complex of scientific research conducted at the VNIIA required for this necessitated constant and thorough work with producers: Their taxonomic status, the stability of

antibiotic formation, and the conditions for maintaining activity had to be revealed, variants had to be differentiated in relation to various characteristics, and so on. Purposeful comparative research accounting for the laws of evolution and the use of large numbers of both species and strains within the same species, but differing in productivity or other characteristics, were especially important in this case. This research enjoyed considerable development in the producer culture laboratory of the VNIIA (V. D. Kuznetsov). In this case the object of analysis was the strains isolated by the institute's research laboratories or acquired on an exchange basis from our country's other scientific institutions and a number of foreign laboratories.

A. A. Prokof'yeva-Bel'govskaya, who worked at the VNIIA for a number of years, made a significant contribution to the study of the cytology and genetics of actinomycetes.

Many years of systematic and purposeful work at the VNIIA resulted in creation of the country's largest collection of soil microorganisms--producers of biologically active compounds. It includes actinomycetes, fungi, and bacteria--producers of hundreds of different antibiotics, producers of enzymes, vitamins, and amino acids, microorganisms capable of transforming steroids, and so on. International standard cultures in the collection, which are provided to laboratories in both our country and abroad, have important significance. The potential of the collection as a source of strains for producing antibiotics and their biologically active compounds is great, and with time this potential will be realized.

As the science of antibiotics and antibiotic industry developed in the USSR, other scientific collectives besides the VNIIA and the USSR Academy of Sciences Institute of Microbiology were established and included in research on ray fungi. Especially significant among them are the USSR Academy of Medical Sciences Institute of New Antibiotics, the Leningrad Institute of Antibiotics (presently the VNITIAF [All-Union Scientific Research Institute for the Production of Medical Antibiotics and Enzymes]), and the Antibiotic Laboratory of Moscow State University.

### III

Significant difficulties associated with a lack of knowledge on the physiological properties of mold fungi and actinomycetes had to be surmounted by scientific collectives and by workers of central plant laboratories and fermentation shops during initiation of antibiotic production.

The foundation for research on penicillin was laid in 1942 under the guidance of Z. V. Yermol'yeva, the properties of producer strains were subjected to systematic study (T. I. Balezina, I. V. Ravich, N. M. Furer), and development of media for their cultivation went on in parallel (M. M. Levitov, V. A. Severin). This research served as the basis for development of domestic fundamental research on the biogenesis of the secondary metabolites produced by mold fungi. The practical result of this research was creation of the

first procedures for obtaining benzylpenicillin using the surface method for culturing the producer in 1944. Antibiotic production based on these procedures was organized at the Chemicopharmaceutical Plant imeni L. Ya. Karpov. The next research stage was associated with development of a sub-surface method for penicillin production (V. I. Zeyfman, R. V. Murakhver, L. M. Utkin, O. B. Gravovskaya, N. K. Solov'yeva). As a result of this work, in 1947-1948 benzylpenicillin production was fully converted to subsurface biosynthesis.

Integrated research on streptomycin began in 1946 (N. A. Krasil'nikov, N. K. Solov'yeva). Production of this antibiotic, the second in significance at that time, was started in 1949-1950 at the Chemicopharmaceutical Plant imeni L. Ya. Karpov, and later at the Moscow Medical Preparations Plant No 1.

It is difficult to overstate the great creative contribution made to creation of antibiotic industry and its successful work by A. G. Natradze, A. P. Grishakova, E. S. Korzhenevskiy, Ye. R. Valashek, I. A. Mayorov, I. M. Tanchenko, D. Kh. Skalaban, and Ye. V. Yakovleva.

Together with the plants, the VNIIA collective grew and acquired experience and scientific authority. Laboratories of the physiology of penicillia (M. M. Levitov) and actinomycetes (A. D. Zamyslov, V. G. Makarevich, N. V. Orlova), biochemistry (V. A. Severin), and experimental technology (B. S. Alejev, S. L. Brinberg, R. V. Murakhver) were organized at the institute. Research was started in 1949 on chlortetracycline and in 1951 on oxytetracycline. Industrial methods for obtaining these antibiotics were developed through integrated research by N. V. Orlova, A. A. Mel'nikova, M. M. Meksin, and L. A. Popova. The plant imeni L. Ya. Karpov began producing chlortetracycline in 1952 and oxytetracycline in 1954.

Many years of research laid the foundation of general physiology of the fungi and actinomycetes, and many features of the metabolism and micromorphology of microorganisms--antibiotic producers--in different stages of their development were studied in connection with culturing conditions. Both the general laws governing antibiotic formation and individual properties of many industrial producer strains were studied (M. M. Levitov, V. A. Severin, N. V. Orlova, S. L. Brinberg, V. G. Makarevich, S. V. Gorskaya, V. A. Gotovtseva, I. I. Tovarova, T. N. Laznikova, L. M. Lur'ye, Z. I. Surikova, I. V. Gracheva, S. V. Dmitriyeva, G. F. Zavileyskaya, M. M. Bychkova, G. D. Pestereva). Processes were successfully developed for biosynthesis of tetracyclines, macrolides (oleandomycin, erythromycin), aminoglycosides (kanamycin, gentamycin), and a number of other antibiotic compounds. Later, the efforts of the scientific collectives were directed toward, in addition to new developments, intensification of antibiotic biosynthesis.

Intensification of antibiotic biosynthesis is significantly or even primarily associated with successes in experimental selection pertaining to creation of highly productive strains of microorganisms, as was demonstrated in the works of S. I. Alikhanyan, S. Yu. Gol'dat, Yu. E. Bartoshevich, I. A. Rapoport, A. F. Teteryatnik, S. Z. Mindlin, A. V. Vladimirov, V. G. Zhdanov, F. S. Kelpikova, and others.



The economic impact from using the new strains is especially noticeable inasmuch as their introduction into production requires practically no additional material outlays. The economic impact from introduction of just a few highly active strains of "high-volume" antibiotic producers into production by workers of the VNIIA was many millions of rubles.

In addition to research aimed at heightening productivity, selection was performed on strains characterized by valuable industrial properties such as lack of pigments, resistance to the inhibitory action of phosphorus, a capability for reducing foaming of culture fluid, and resistance to phages.

As we know, alteration of a producer's genome leading to intensification of antibiotic formation could be achieved in several ways: By combinational regrouping of genes, enlargement of the number of chromosomes (polyploidy) or the number of copies of individual genes and plasmids containing genes responsible for antibiotic synthesis and, finally, by altering genes through the action of mutagens governing the intensity with which the antibiotic compound is biosynthesized. In view of the methodological difficulties of identifying recombinants (the first way) and the fact that work on actinomyces plasmids had only started recently (as was true in general of the initial period of development of genetic engineering--construction of plasmids, their release from control by the cell's regulatory mechanisms, and so on--the second way), the third way--achievement of induced mutations and selection of mutants characterized by higher productivity--has played the basic role in practice. This way has made it possible to heighten the activity of the producers of the principal industrially produced antibiotics by many times within a short time.

The last stage--evaluation of the strains--continues to be highly laborious despite certain successes that have been achieved in automating the laboratory work. The need for studying the relationship between "supersynthesis" of antibiotics and the specific features of basal metabolic processes in mutant strains of this sort is becoming increasingly more pressing today. Success in the appropriate research may permit us to evaluate the promise of a new strain in a new way. Thus data on the relationships between heightened synthesis of fusidine and one of the two alternative electron transport chains in the mycelium of the producer of this antibiotic have been obtained in joint work by two VNIIA laboratories--the laboratory of genetics and selection, and the laboratory of biomolecular research. The data indicate a possibility for introducing more efficient preliminary selection of mutants according to fundamentally new characteristics into selection work.

Analysis of the permeability of the cytoplasmic membrane and of permeases located within it is of no little interest to determining the promise of selected mutants. The preliminary data attest to existence of correlation between changes in some membrane properties and the quantity of antibiotics in the culture fluid. Development of selective procedures for achieving regulatory mutations coupled with disturbance of retroinhibition, catabolite repression, and change in the translation mechanism should be thought of as practically important.

Finally, we should not fail to note that fundamental research conducted in recent years on extrachromosomal heredity has attracted attention to actinomycete plasmids. Evidence is being presented that in some cases genes that encode formation of enzymes catalyzing reactions in biosynthesis of individual antibiotics are located in plasmids. It is extremely important to find ways in the future to influence the mechanisms of intracellular regulation controlling replication of plasmids in actinomycetes and their state, be they integrated with chromosomes or in independent form. It is not excluded that new possibilities for "supersynthesis" of antibiotics may be found in this case.

Physiological research on new producer strains has had great significance to intensifying antibiotic biosynthesis. This research has made it possible to determine the requirements of the strains and reveal optimum conditions for biosynthesis of antibiotics by each concrete strain. We can conclude from research on a large number of strains producing the same antibiotics that different strains differ significantly and that different culturing conditions would be required for formation of a maximum quantity of antibiotics.

Intensive research has been going on for a number of years at the VNIIA with the goal of developing the procedures of regulated fermentation making it possible to significantly heighten antibiotic biosynthesis in production conditions. Through constant control and maintenance of the concentrations of different nutrient components at optimum levels for antibiotic biosynthesis, which is achieved through periodic addition of these components, we can lengthen the productive phase of mycelium development and avoid the unfavorable effect of excessively high initial nutrient concentrations. Concurrent optimization of production parameters in application to different phases of mycelium development also plays an important role in this case. Considering the mutual influences of different factors during fermentation and other circumstances causing complications, we should recognize it especially suitable to make broad use of mathematical methods in experiment planning. The effectiveness of these methods has been confirmed in many concrete cases of the practical work of the VNIIA in recent years.

Experience accumulated at the VNIIA has made it possible to initiate creation of standard methods on the basis of which we can unify the approaches to developing the procedures of regulated fermentation for the purpose of antibiotic acquisition. The greatest success in regulated fermentation at the VNIIA and at the plants of the subsector were achieved in penicillin production. Conditions have been created permitting maintenance of a mycelium, rich in nitrogen-containing compounds and having high productivity, in culture. The activity of culture fluid has been heightened dramatically as a result of development of the method of regulated fermentation (M. M. Levitov, L. M. Lur'ye).

The methods of regulated fermentation are being used successfully not only to acquire penicillin: The VNITIAF and the Riga Medical Preparations Plant have proposed an effective method for regulated biosynthesis of griseofulvin.

Regulated fermentation is being employed in the production of tetracycline (V. G. Makarevich), and erythromycin (S. L. Brinberg).

However, achievements in regulated fermentation have posed a new problem to researchers. Accumulation of antibiotics in culture fluid at concentrations of several thousands to several tens of thousands of micrograms per milliliter has been found to be of consequence to the producer. Research on the mechanism behind the influence of antibiotics on their producers and, more precisely, on their biosynthesis has the goal of developing ways to prevent this phenomenon, which may be both indirect (inhibition of biosynthesis of macromolecules in general, to include enzymes participating in formation of the antibiotic) and direct (selective inhibition of antibiotic formation following the feedback principle).

Many years of experience have shown that antibiotic biosynthesis is most intensive as a rule not in synthetic but rather in complex nutrient media of complex organic composition. This circumstance raises a number of problems before fermentation shop workers and VNIIA physiologists associated with the nonstandard nature of some raw materials (corn extract for example) and with the need for substituting raw materials that are valuable food products, or which are in short supply or expensive. As a result of a great amount of research conducted by the VNIIA in cooperation with the plants, we have been able to considerably standardize biosynthesis using organic raw materials of varying composition.

At the same time when we replace traditional nutrient medium components we must consider not only the principal characteristic--the activity of the culture fluid--but also a number of its other characteristics, inasmuch as the rheological properties of the medium, foaming intensity, the concentration of solid particles, and so on influence not only the initial stages of processing the culture fluid and its filtration but also, in the end, the quality of the antibiotic preparation itself.

It is fundamentally important to seek new raw materials among the end products and intermediate products of "big chemistry," petrochemistry in particular. However, in this case we would have to devote special attention to the possible toxic properties of the compounds employed.

Finally, systematic work with some wastes of biosynthetic production operations (the mycelial mass, and others) as possible raw material sources is now being placed on the agenda. Apparently this would require a more careful approach to and research on the methods for processing the wastes undergoing testing.

The laboratory of antibiotic biosynthesis at the VNIIA has made certain achievements in replacing traditional raw materials. This work must be continued and broadened in the future.

Discussing the longer-range future of antibiotic biosynthesis, we should point out that it is difficult to view the enzymatic reactions of the final stages of "assembly" of the antibiotic molecule, and their sequence in

particular, as differing significantly in relation to the particular media employed. However, the process of biosynthesis can be viewed as biosynthesis of not only the molecule itself but also its precursors. These "preliminary" stages of biosynthesis must also be studied at the molecular level, concretely in this case, in application to those initial compounds, transformation of which begins biosynthesis. What we need here is a closer relationship between studies which from a methodological standpoint have a "molecular nature" and the objects and processes actually existing in the industrial fermenter, in which biosynthesis proceeds in a medium of composition governed not only by the specific physiological features of the producers but also by economic and technological feasibility.

This approach would be possible only on the condition of broad multipurpose use of radioisotopes and stable isotopes in the research. The problem of modeling the production conditions for the purposes of biomolecular research is acquiring important significance in this connection. As an example the VNIIA has found a sufficiently good solution to the problem of using radioisotopes to study the hydrodynamic conditions in fermenters containing real culture fluids (Yu. O. Sazykin, Ye. S. Bylinkina).

Major successes in research on intercellular regulation of biosynthetic processes making it possible to reveal some of its mechanisms have been attained in recent years in molecular biology. However, the workers of sector institutes must apply a great deal of effort to make concepts of molecular biology such as, for example, "catabolite repression" or "allosteric regulation of enzyme action," which are applicable to the classical objects of molecular biology and genetics, less abstract and more applicable to the tasks of intensifying antibiotic biosynthesis.

An approach to studying the mechanism behind antibiotic formation based on the idea that antibiotics are factors regulating biosynthesis of macromolecules in the mycelium of the producer perhaps deserves development today. This idea is hardly valid in relation to all industrial antibiotics, but perhaps it does apply to, for example, biosynthesis of aminoglycosides. The mechanisms of reversible inactivation of aminoglycosides by means of phosphorylation and acetylation have been revealed in the mycelium of their producers. It has been shown many times that the inability of derivatives phosphorylated by the mycelium's phosphotransferase to bind with ribosomes and inhibit protein synthesis can be corrected by the action of phosphatase.

Finally, though it may appear to be something of the distant future, it is entirely realistic that we will be able to make industrial use of a successive series of immobilized enzymes catalyzing individual reactions in synthesis of the antibiotic molecule--that is, we will be able to achieve entirely acellular antibiotic synthesis not in the laboratory but in production conditions.

#### IV

Swift growth in antibiotic production elicited a need for creating and developing biotechnology. This problem is being worked on by a number of institutes of the USSR Academy of Sciences and by sector scientific institutions. The foundation of this new research direction was laid in the 1950's at the VNIIA. This research includes thorough study of the technology of biosynthesis itself, numerous auxiliary processes preceding biosyntheses, and the processes of isolating biosynthetic products.

I. I. Gel'perin systematically participated in organization and development of technological research at the VNIIA for 30 years. The technological division of the VNIIA grew out of the antibiotic laboratory of the All-Union Scientific Research Chemicopharmaceutical Institute headed by V. I. Zeyfman. Work on apparatus to support antibiotic biosynthesis was started in this laboratory. T. T. Filippov'yants conducted research on the process for benzylpenicillin extraction, I. V. Lyskovtsev developed separating and, later, extracting equipment, the Rossiya extractor in particular, and Z. Ye. Posdnyakova, I. V. Rozovskaya (Korshun), and Ye. S. Bylinkina did successful work on desiccation of antibiotic solutions. In the period between 1949 and 1964 technological research was guided by R. V. Murakhver, I. M. Petrov, T. T. Filippov'yants, and I. D. Boyko, who had made a substantial contribution to solving a number of the problems of greatest importance to antibiotic industry. Later, in 1966, the laboratory of biotechnological processes headed by Ye. S. Bylinkina and the laboratory of chemotechnological processes headed by S. A. Zhukovskaya were created at the VNIIA in correspondence with the two fundamental directions in antibiotic production technology.

During the last decade, the laboratory of biotechnological processes completed a cycle of research on the mechanisms behind mass exchange in triphasic systems and on the hydrodynamic working conditions of fermenters. Note should be made of systematic and productive research on the criteria of measure conversion. Procedures have been developed for determining and calculating hydrodynamic conditions and the conditions for mass exchange in fermenters, which made it possible to optimize their design (L. D. Shtoffer, Ye. S. Bylinkina, T. S. Sherstobitova). Developments of the VNIIA in this area have been implemented in part at the subsector's plants, and a plan for their subsequent introduction has been written.

Considering the importance of the problem, significant attention has been devoted to regulating foam formation. The search for effective foam suppressors, which went on for a number of years at the VNIIA (R. D. Soyfer), made it possible to both recommend fundamentally new foam suppressors (B-400 propynol) and broaden the assortment of silicone foam suppressors. Nevertheless the search for new synthetic foam suppressors to replace natural fats continues to be a pressing task. The need for continuing research on the effect of foam suppressors on mass exchange during fermentation is sufficiently obvious as well.

Cleaning and sterilization of air in the production atmosphere occupies a significant place in the complex of technological research (G. L. Motina). The complex of research on air sterilization includes development of new, highly effective filtering materials and filter designs, development of original methods for periodic and continuous monitoring of air purification systems in production, research on filter aerodynamics, and so on.

Organization of systematic research on the effect of production parameters upon biosynthesis has necessitated development of special instruments, sensing units, control methods, and ways for using computers in the work. In 1970 the VNIIA organized the laboratory of automation and computer technology, which is conducting research on automation of production processes and experimental projects, on application of mathematical methods and computers, and on modeling and optimization of production processes (V. V. Biryukov).

Creation of automated systems by which to control production processes evolved in antibiotic production is becoming an increasingly more pressing task. The VNIIA's laboratory of automation and computer technology is conducting concrete research in this area together with the Kurgan Sintez Combine and a number of scientific research institutions.

A significant volume of technological research being conducted at the VNIIA is devoted to isolation and chemical purification of antibiotics (S. A. Zhukovskaya and others).

A complex of research on coagulation and filtration of culture fluids has been conducted at the laboratory. Effective methods have been developed for preparing fluids prior to filtration making it possible to intensify the subsequent production stages in application to production of 14 different antibiotics. A unified, sensible procedure for filtering culture fluids and native solutions which includes waste processing has been developed (O. S. Lin'kova). Research has been conducted on flocculation, and a principle for effective purification of native solutions using polyelectrolyte flocculants has been suggested (L. M. Vernikova). The search for optimum apparatus for ion-exchange processes has led to creation of a system of continuously operating columns used to sorb compounds both from native solutions and culture fluids (L. M. Klyuyeva). Factors limiting antibiotic extraction have been revealed and the ways for intensifying this process have been determined on the basis of research on the statics and kinetics of antibiotic extraction. Optimum conditions for extraction of antibiotics insuring the greatest selectivity of the process have been discovered. An abbreviated procedure for purification of benzylpenicillin by extraction, characterized by a larger antibiotic yield and requiring fewer production stages, has been developed. Work is being done to create effective domestically-produced equipment for antibiotic extraction jointly with the USSR Ministry of Chemical and Petroleum Machine Building.

Work is being done in the laboratory on a progressive method for membrane purification and concentration of the products of microbiological synthesis (L. L. Stremovskiy), and research is being conducted to improve the quality of the end product (L. A. Moiseyenko).

In the last 5 years the laboratory has organized the work of regenerating organic solvents with the purpose of improving environmental protection, heightening production safety, and reducing the materials-intensiveness of production (T. V. Torgovanova).

Much experience has been accumulated by the technological division of the VNIIA in desiccating antibiotics by atomization, sublimation, and with the use of a suspended or fluidized bed (D. F. Filorik'yan). The task today is to develop and begin series production of drying units satisfying the specific requirements of antibiotic production jointly with specialized planning and design organizations.

The VNIIA is conducting technological research in integration with institutes of other sectors and departments. Division consultants N. I. Gel'perin and V. V. Kafarov are providing constant assistance to the technological division of the VNIIA.

## V

Acquisition of highly purified antibiotic preparations requires the use of complex chemical methods and conduct of diverse chemical research; this is why a chemistry division was created at the VNIIA (M. M. Shemyakin). Later a number of specialized laboratories were created at the VNIIA--antibiotic isolation and purification (D. M. Trakhtenberg), antibiotic chemistry (I. A. Red'kin, A. S. Khokhlov, and later A. D. Kuzovkov), physical chemistry (B. P. Bruns, Ye. M. Savitskaya), and analytical chemistry (V. B. Korchagin). The results of research conducted by these laboratories were placed at the basis of methods for producing the most important natural antibiotics--penicillin, streptomycin, erythromycin, oleandomycin, tetracyclines, kanamycin, fusidine, and novobiocin. A great contribution to development of the procedures was made by colleagues of these laboratories--N. M. Vikhrova, S. I. Kaplan, S. I. Mamiofe, I. I. Inozemtseva, L. F. Yakhontova, G. S. Libinson, L. V. Birlova, E. I. Rodionovskaya, Z. T. Sinitsina, and G. S. Rozenfel'd.

The interests of medical practice elicited a need for developing research on chemical transformation of natural antibiotics having new valuable properties. Laboratories and specialized groups were created at the VNIIA to obtain semisynthetic antibiotics. A cycle of research aimed at creating semisynthetic penicillins had highly important practical significance in this case. This research necessitated development of production methods for obtaining 6-APK, creation of a number of other types of intermediate products, particularly some fatty-aromatic acids and amino acids, and development of methods for synthesizing the end products. This research, which was conducted

jointly by colleagues of a number of laboratories (M. M. Levitov, Ye. M. Savitskaya, I. T. Strukov, M. S. Rabinovich, M. A. Panina), led to development of the theoretical grounds for the process and for organization of industrial production of semisynthetic penicillins of greatest importance to medical practice--methicillin, oxacillin, ampicillin, and others.

Research conducted by the laboratory headed by A. D. Kuzovkov (T. A. Ushakova, N. V. Shcheberstova) on the chemistry of tetracyclines and on methods for their transformation made it possible to develop methods for acquiring semisynthetic preparations such as metacycline and doxycycline, so needed by practical medicine.

A complex of projects is presently being conducted to organize production of semisynthetic derivative cephalosporins from both cephalosporin C and 7-ATsK on one hand and 7-ADTsK on the other (Yu. E. Bartoshevich, A. S. Mezentsev, S. A. Zhukovskaya, L. M. Klyuyeva, A. D. Kuzovkov, Ye. M. Savitskaya).

Beginning in 1952-1953, the laboratory of physical chemistry (headed first by B. P. Bruns and later by Ye. M. Savitskaya) began conducting fundamental research on ion exchange of organic compounds in synthetic ion-exchange resins. Many years of research on sorption of organic compounds, conducted in close contact with specialized institutions of the USSR Ministry of Chemical Industry involved in development of synthetic sorbents, led to discovery of the fundamental laws governing ion exchange of organic ions. The specific features of the kinetics and equilibrium of such systems were revealed and studied for the first time (B. P. Bruns, Ye. M. Savitskaya, L. F. Yakhontova). The dependence between the kinetics of the process and the selectivity of exchange was determined (B. P. Bruns, G. S. Libinson, A. V. Mikhalev). The general theory for calculating equilibriums pertaining to ampholyte sorption was worked out (Ye. M. Savitskaya, P. S. Nys). Decomposition of antibiotics in the ionite phase was discovered, and these catalytic processes, which have extremely important significance to industrial use of ionites to isolate antibiotics, were studied (B. P. Bruns, Ye. M. Savitskaya, K. I. Surkova).

Special lots of the sorbents intended for medical industry alone were developed on the basis of the theory of organic compound sorption jointly with enterprises of the USSR Ministry of Chemical Industry (L. F. Yakhontova, Ye. M. Savitskaya). Domestically produced sorbents developed as a result of this integrated research are now being used in antibiotic production.

The laboratory of physical chemistry has developed a number of original ion-exchange methods for obtaining antibiotics and organic compounds. These methods have been introduced into industry (L. F. Yakhontova, Ye. M. Savitskaya). New, effective brands of sorbents are being offered to antibiotic industry.

Work to create the physicochemical grounds for enzymatic transformation of antibiotics and their intermediate products was started in 1972 (M. M. Levitov, Ye. M. Savitskaya, P. S. Nys). Profound research is being conducted on the mechanism behind biocatalysis and immobilization of enzymes of microbial



origin (P. S. Nys, N. N. Shchellenberg). Original biocatalytic methods for obtaining 6-APK and other intermediate products used in the synthesis of antibiotics in the penicillin and cephalosporin series have been developed. The Soviet Union's first industrial enzymatic production procedure--acquisition of 6-APK--was introduced into medical industry (VNIIA, Riga Medical Preparations Plant, Tallin Polytechnical Institute). The economic impact from this method is very large, and the process is coming close to being wasteless.

In 1976 the VNIIA was awarded the Perpetual Red Banner of the CPSU Central Committee, the USSR Council of Ministers, the AUCCTU, and the Komsomol Central Committee for solving one of the most important national economic problems in the project "Development of the Industrial Procedures for Obtaining Native Penicillinacylase, Immobilized Acylase, and 6-APK," for which the VNIIA was the head organization.

In 1976 the laboratory of physical chemistry was reorganized as the laboratory of sorption and biocatalysis. The principal scientific problems being worked on by the laboratory are research on sorption and biocatalysis and creation of new progressive sorption methods for isolating antibiotics and methods for obtaining both the antibiotics themselves and their key intermediate products through enzymatic transformation.

Owing to the work of the laboratory of analytical chemistry (headed by V. B. Korchagin), the greater part of the biological methods for analyzing antibiotics have been substituted by modern physicochemical methods. The laboratory is successfully developing control methods based on infrared spectroscopy (N. B. Dzegilenko), electrochemical titration (V. I. Vasil'yev), various chromatographic methods (Z. Ye. Vtorova, I. M. Vagina), and ultraviolet spectrophotometry and enzymatic reactions (N. S. Moroz, V. N. Korobkin, D. E. Satarova). The laboratory is providing constant scientific-technical guidance to the analytical services of the subsector's plants. Together with other specialists of the VNIIA, the laboratory's colleagues took an active part in preparing the 10th edition of the USSR State Pharmacopoeia.

Modern physicochemical methods of analysis based on laboratory methods developed at the institute and at the plants were introduced. These methods make it possible to control antibiotic production from the stage of antibiotic biosynthesis or synthesis to the output of the end product, create optimum industrial processes for producing high-quality preparations, develop appropriate scientific-technical documents, and monitor the correspondence between the quality of the antibiotics and today's requirements.

Development of ready-to-use medicinal preparations that are optimum in relation to stability, biological activity, and other characteristics and intended for various means of introduction into the patient's body or for special purposes (for example, for use in pediatrics, in the otorhinolaryngological clinic, in the eye disease clinic), is a necessary part of research accompanying introduction of an antibiotic into medical practice. Medicinal forms of

all of the most important antibiotics produced by medical industry were created in many years of research by the VNIIA's laboratory of ready-to-use medicinal preparations, organized on the initiative of Z. V. Yermol'yeva and headed for many years by Ye. N. Lazareva (O. P. Belozeroва, L. A. Aver'yanova, V. F. Okhotnikova, I. P. Kutsкая, L. A. Kovaleva, E. V. Kagan). In addition to conducting purely pharmaceutical research, this laboratory obtained a number of derivative antibiotics from the streptomycin and tetracycline group, and it created combined antibiotic preparations satisfying the needs of combined chemotherapy. In recent years this laboratory (headed by L. K. Grakovskaya) has been working on medicinal preparations of new antibiotics, it is improving the industrial processes for producing preparations with the purpose of upgrading their quality, and it is expanding biopharmaceutical research. A new direction in creation of medicinal antibiotic preparations was development, under the guidance of S. I. Eydel'shteyn, of their aerosol forms in cans. Production of antibiotics as aerosols makes it possible to significantly heighten their effectiveness in some areas of medical practice.

The interests of continually growing antibiotic production have necessitated organization of special scientific subdivisions in the VNIIA. The division (laboratory) of technical-economic research, which was established and headed for many years by S. I. Maymind, occupies a special place among them. In this laboratory (V. V. Andreyeva), systematic technical-economic analysis is being performed on the production activities of plants, particularly on the cost of the products, the perspectives for the subsector's development are being forecasted, wholesale prices are being reviewed, future demand for raw materials and materials is being determined, and the technical-economic standards for the planning, distribution, and use of raw materials in antibiotic production are being developed.

The laboratory of labor hygiene, industrial toxicology, and safety, organized and headed by G. B. Shteynberg, is performing extensive tests on industrial antibiotic production processes, it is revealing unfavorable production and occupational factors, and it is developing ways to exclude or limit the effects of these factors on workers.

The laboratory of waste water and atmospheric discharge treatment (V. F. Karpukhin) was created at the VNIIA in response to the national significance of the environmental protection problem, and it has been making a continually greater contribution to the subsector's development.

The specific features of biosynthetic acquisition of antibiotics is such that, as the experience of various countries shows, more than 99 percent of the raw materials used turn out as production wastes. Consequently there are many possibilities here for recycling of many raw materials both by antibiotic industry itself and by other sectors of the national economy.

As we know, creation of wasteless production procedures has been declared to be a national task in decisions of the 25th CPSU Congress. Production

organized into a closed cycle not only results in use of natural resources with maximum economy but also solves the problem of protecting the environment from contamination by production wastes. In this connection we will need to develop a complex of technological and sanitary-hygienic measures to bring the wastes to the required level in quantitative and qualitative respects with an eye on creating wasteless production operations in the future. Correspondingly, we must thoroughly analyze the liquid, solid, and gaseous wastes of antibiotic production, and we must develop methods to treat and utilize wastes with a consideration for the real possibilities of both the present and future. The great deal of work being done in this area at the VNIIA is already enjoying direct implementations at the subsector's plants.

The activities of the VNIIA as the head institute of antibiotic industry have always been organically united with production. Close ties between science and production, which have been undergoing development and strengthening in the last few decades, have been and continue to be the indispensable basis for work of the entire VNIIA collective. The forms of these ties are diverse--technical assistance to plants introducing the institute's scientific development, contracts for cooperation, business contracts, specialist training, and so on. In recent years joint research, conducted after selection of the objective at the very beginning of the work, is starting to occupy a continually greater place. Scientific management of central plant laboratories and detailed coordination of research with the plants are making it possible to reduce development time and improve the quality of production documents and the products. This approach is all the more natural because highly qualified researchers have been trained at the plants, capable of solving complex scientific-practical problems (G. I. Kleyner, L. P. Chumakova, V. M. Orekhova, M. A. Bogatskiy, V. F. Belyanina, A. I. Berezovskaya, A. V. Unegov, N. D. Koval'chenko, M. G. Gandman, T. G. Borisova, A. I. Parfenova, L. N. Preobrazhenskiy). Specialists such as A. V. Savitskiy, Z. I. Shelomova, E. I. Daugovet, N. M. Matokhina, L. P. Telegin, B. V. Pestov, G. A. Andriyevskiy, I. T. Butsenko, A. N. Polunin, G. A. Pominal'nik, I. A. Orlov, D. I. Shvedov, B. N. Krupnov, and I. Ya. Khoroshutin have acquired a considerable amount of experience at enterprises of antibiotic industry, and they have become prominent production organizers.

By as early as in the Tenth Five-Year Plan domestic medical industry has provided the world's most important and most effective antibiotics to public health. In this case more than 95 percent of all antibiotic preparations and their medicinal forms presently in production are being produced in accordance with procedures created by the VNIIA in cooperation with the subsector's plants; the volume of this production, in financial terms, was more than 1 billion rubles in the five-year plan.

## VI

The historic decisions of the 24th CPSU Congress placed a task of priority importance before Soviet antibiotic science and production--finding new

antibiotics effective against stable forms of microorganisms, malignant tumors, and viral diseases. The VNIIA's research system was reorganized: Laboratories searching for new antibiotics were significantly reinforced by personnel and outfitted with unique equipment. We should not fail to note that new antibiotics had been sought successfully in the previous periods of the institute's development (N. K. Solov'yeva, Z. E. Bekker, T. P. Suprun). Original antibiotics discovered earlier at the VNIIA--al'bofungin, aktinoksantin, reumitsin, and some others--were studied in detail by M. N. Kolosov, S. Ye. Yesipov, and A. S. Khokhlov at the USSR Academy of Sciences Institute of Bioorganic Chemistry and the USSR Academy of Sciences Institute of Biochemistry and Physiology of Microorganisms. In the last 2 years the volume of work pertaining to the search for new antibiotics has grown considerably at the VNIIA. Chemical research on new antibiotics is proceeding more intensively at the VNIIA. There are a number of antibacterial and antitumor preparations in various stages of study today.

Close ties not only with production but also with medical practice have always been typical of the VNIIA. These traditions were established upon organization of the VNIIA's division of experimental therapy by Z. V. Yermol'yeva and A. P. Avtsyn (presently the division of experimental biology headed by S. M. Navashin). The division contains the following laboratories: Experimental chemotherapy (I. P. Fomina), cytology, together with an electron microscopy group (Ye. K. Berezina), pharmacology (V. N. Solov'yev), and biomolecular research (Yu. O. Sazykin). Colleagues of the VNIIA's biomedical laboratories are conducting the entire complex of preclinical research on antibiotics and their numerous medicinal forms, which is necessary before the preparations could be tested in the clinic. The specific properties of antibiotics and their effects on various organ systems and tissues are being studied in detail by the VNIIA's biomedical laboratories in connection with the growing demands the USSR Ministry of Public Health is placing on the quality of antibiotic preparations. This has necessitated assimilation of new types of experimentation with animals and inclusion of additional methods for studying mutual relationships antibiotics have with microorganisms and macroorganisms (A. I. Semich, M. A. Petrova, K. I. Germanova).

A major program of research on the genetic and biochemical mechanisms behind the resistance of pathological agents isolated from patients has been started by the laboratory of experimental therapy jointly with the laboratory of biomolecular research in connection with the importance of the problem of microorganism stability to public health practice and production. Special attention is being devoted in this case to extrachromosomal stability factors (plasmids). The specific mechanisms behind enzymatic inactivation of the most important groups of antibiotics--betalactamides and aminoglycosides--are being studied. This research direction, which has fundamental significance, is creating a sensible foundation for research on new effective antibiotics and directed chemical transformation. Detailed analysis of the kinetics behind distribution of antibiotics and their medicinal forms within the body is acquiring increasingly greater significance (V. G. Koroleva).

Labeled antibiotic preparations, being obtained at the VNIIA and employed in joint research by a number of laboratories (N. S. Gryaznova), are playing an important role in research on the mechanisms behind antibiotic resistance of microorganisms and enzymatic transformations of antibiotics in animal tissues.

The VNIIA's division of experimental biology is closely associated with many of the leading clinics, institutions, and agencies of the public health service. When preparations are subjected to clinical study, the research is conducted jointly with physicians of different specialties, which makes it possible to thoroughly describe the preparation and elaborate upon the indications for its use and its method of use. The VNIIA has strengthened its traditional ties with the leading institutions, such as the Institute of Clinical and Experimental Surgery (V. V. Petrovskiy), the Institute of Surgery imeni A. V. Vishnevskiy (M. I. Kuzin), and the Central Institute of Epidemiology (V. I. Pokrovskiy), as well as with the leading clinics founded by I. A. Kassirskiy, V. Ya. Shchlapoberskiy, B. Ye. Votchall, G. P. Rudnev, and A. F. Bilibin. Joint research on antitumor antibiotics with the Oncological Scientific Center (N. N. Blokhin) and other oncological institutions is developing successfully.

The institute prepares and systematically publishes a large volume of scientific literature providing information to physicians on the characteristics of new antibiotics, and it writes instructions and methodological directions on their use. The experience of experimental clinical study of antibiotics has been generalized in the "Spravochnik po antibiotikam" (Antibiotic Handbook) (3d edition) and in the monographs "Polusinteticheskiye penitsilliny" (Semisynthetic Penicillins), "Antibiotiki gruppy aminoglikozidov" (Antibiotics of the Aminoglycoside Group), and others.

Considering the tasks of the Tenth Five-Year Plan--the five-year plan of effectiveness and quality, the significance of standardization and a systems approach to work on production processes and to heightening preparation quality is growing especially (V. M. Kantere, A. P. Arzamastsev). The requirements being imposed on scientific-technical documents written at the institute are growing significantly and the role of control laboratories, particularly the laboratory of microbiological control (S. M. Chaykovskaya) and the laboratory of analytical chemistry (V. B. Korchagin) is intensifying in this connection. Constant, purposeful work done by control laboratories jointly with the authors of the preparations and plant workers has led to a dramatic rise in the quality of antibiotics, which now satisfy the stiff requirements of the modern Pharmacopoeia. In this connection we should not fail to note the great amount of work invested into the organization and work of control laboratories by L. M. Yakobson, A. Ye. Tebyakina, Ye. N. Druzhinina, and A. N. Shchneyerson.

Exports of domestic antibiotics are constantly growing. The VNIIA holds patents in various countries on both the processes for acquiring a number of antibiotics and the compounds themselves. Licenses for industrial production

of antibiotics are being sold abroad. The institute's international ties are growing and developing. An important task of the VNIIA is coordination of antibiotic research by CEMA countries: Mutually advantageous scientific-technical cooperation of Soviet scientists with scientists of Bulgaria, Hungary, the GDR, Poland, Romania, Czechoslovakia, Yugoslavia, and other socialist countries is expanding. Scientific and business contacts are being developed successfully with research institutes and companies of England, Italy, the USA, France, Sweden, Japan, and other countries.

New, important tasks face Soviet public health and medical industry. Complying with the decisions of the 25th CPSU Congress, the workers of science and industry are making their contribution to the common labor of our people directed at attaining the effectiveness and quality required by the five-year plan. Considering the great importance of antibiotics to medicine and the national economy, in 1977 the Presidium of the USSR Academy of Sciences and the USSR Council of Ministers State Committee for Science and Technology held a coordinating conference devoted to the most pressing scientific and practical aspects of the antibiotic problem jointly with executives of the USSR Academy of Medical Sciences and a number of ministries and departments, and scientists and workers in industry.

The conference adopted a resolution foreseeing a program of measures directed both at broadening antibiotic research and at accelerating introduction of the achievements of science into Soviet public health practice and industry.

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EFFECTS OF ELECTROMAGNETIC WAVES ON PRODUCTION OF PROTEASES WITH FIBRINOLYTIC ACTIVITY IN *ASPERGILLUS ORYZAE* (AHLB.) COHN (STRAIN OF MOSCOW STATE UNIVERSITY)

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[Article by N. S. Yegorov, M. B. Golant, N. S. Landau, G. M. Okhokhonina, N. A. Sycheva and A. K. Bryukhova, Moscow State University imeni M. V. Lomonosov, Department of Microbiology, submitted 28 Apr 76]

[Text] Among the enzymes used in man's practical endeavors, proteolytic enzymes occupy one of the principal places; there are applications thereof in various branches of the national economy, medicine and solving many problems of theoretical enzymology. The ever increasing need for proteases advances to the fore the question of finding new and highly active producers, particularly among microorganisms, as well as methods of intensifying production of proteolytic enzymes by these microorganisms.

Chemical or physical mutagens, or else the combination of chemical and physical factors, are used to increase the yield of enzymes. However, under the influence of potent factors, even the specimens that survive and mutate are so damaged that they represent defective, poorly growing forms that require rather complicated media for their development.

In this study, we used electromagnetic waves in the millimeter range, which do not have as severe an effect on the organism as ultraviolet, x- and  $\gamma$ -rays, as the factor used on *Aspergillus oryzae* (Ahlb.) Cohn (MGU [Moscow State University] strain), which is a producer of proteases with fibrinolytic action (Lindauer et al., 1974; Chernova, 1975).

We used *A. oryzae* (MGU strain) mold fungus, cultivated on Czapek medium, as the producer of fibrinolytic enzymes.

To investigate the effects of electromagnetic waves in the millimeter range on production of proteases, a sporulated suspension of this fungus in liquid wort was exposed to irradiation for 3 h from an OV-12 lamp (flux density of 0.1 mW/cm<sup>2</sup>). In subsequent exposures (3-, 4- and 10-fold), the spores treated with electromagnetic waves were cultivated on agarized Czapek medium for 7 days, after which the spores were collected and exposed to irradiation

in liquid wort for 3 h again. The control culture was replated on agarized Capek medium the same number of times as the irradiated one.

The submerged method was used to cultivate inoculum to determine the capacity of the fungus to produce proteases; this was done for 2 days on liquid 4-point wort and the material was added to the experimental medium in amounts of 5 vol.%. The experimental medium we used was one that we selected previously, a synthetic medium with glycerin. The experiments were conducted with the use of submerged cultivation on circular rockers (220-220 r/min) at 28-30°C (Yegorov et al., 1976).

Table 1. Effects of millimeter range of electromagnetic waves on synthesis of proteases with fibrinolytic activity by *A. oryzae* (MGU strain)

Culture	Cultiv. time, h	Bio-mass (mg%)	pH	Fibrinolytic activity		Fibrinol. productivity		Caseinolytic activity	
				arbitr. units/ml	%	arb.un/ml mycelium	%	units/ml	%
Base	72	866	6.6	347	100	40.0	100	0.62	100
	120	1286	6.6	371	100	28.9	100	0.78	100
	168	706	6.5	446	100	63.2	100	0.90	100
Irradiated	72	900	6.6	424	122	47.1	117	0.62	100
	120	900	6.6	447	120	45.2	156	1.24	158
	168	468	6.45	644	144	137.6	217	0.93	103

In the course of development of the fungus, we measured the Ph with a potentiometer, biomass by the weighing method and fibrinolytic activity by the method of Astrup and Mullertz (1952) on fibrin plates in 6 and 18 h of incubation at 37°. Caseinolytic activity was measured by the method of Sgouris (Sgouris et al., 1961) taking into consideration the increment of tyrosine, using a spectrophotometer at 280 nm, with hydrolysis of casein under the influence of the enzyme. We took the amount of enzyme, 1 ml of which elicited zones of lysis of fibrin per 10 mm<sup>2</sup> as the unit of fibrinolytic activity, and the amount of enzyme which elicits a tyrosine increment corresponding to 450 µg acid-soluble tyrosine in 60 min at 37° in a 4% casein medium as the unit of caseinolytic activity.

The data submitted in the tables constitute the means of 3-4 experiments, and each set was checked for the absence of so-called deviating variants by the method of I. P. Ashmarin et al. (1975) with a reliability level of 95%.

The tested fungus was exposed to electromagnetic waves in the millimeter range which do not elicit a thermal effect in biological objects, do not break chemical bonds and do not destroy cell structures, unlike electromagnetic waves at longer wavelengths, γ-rays, ultraviolet rays and x-rays. However, the change they elicit in polar orientation of molecules in the



organism leads to specific and appreciable changes in metabolism, which are reproducible. According to the literature (Manoylov et al., 1967), the biological effect of nonthermal electromagnetic waves in the low-energy millimeter range is equivalent to hard radiation of 10,000 R.

In view of this possibility of altering the metabolism of microorganisms in the required direction, it was first necessary to establish the effects of electromagnetic radiation on biosynthetic activity of *A. oryzae* (MGU strain). The obtained data (Table 1) indicate that, as compared to the base culture, the irradiated one secretes 1.5 times more proteases in the culture fluid, with both fibrinolytic and caseinolytic activity. The increase in proteases is observed against the background of good growth of both cultures of the fungus, i.e., radiation does not elicit appearance of poorly growing defective forms.

Estimation of fungus productivity according to fibrinolysis is also indicative of the overt advantage (1.5-2-fold) of the irradiated variant over the control. In both cultures, maximum fibrinolysis is observed on the 7th day, when overt signs of autolysis of the fungus appear. Caseinolytic activity reaches a maximum on the 7th day in the base strain, and it is related to cell lysis, whereas in the irradiated strain maximum caseinolysis occurs on the 5th day, when the culture is still at the stationary phase of growth.

Most likely, such differences between the base and experimental variants of the fungus are attributable to the fact that, in the case of irradiation, there is a change not only in quantity, but quality of the protease complex formed by the fungus. This is reflected by the change in correlation between caseinolysis and fibrinolysis.

As we know from the literature, the nature and severity of biological effects of weak electromagnetic fields are largely determined by their parameters. In particular, even negligible changes in wavelength could lead to a sharp change in extent and even direction of the biological effect. A study of the effect of electromagnetic wavelength on production of proteases by a culture of the strain in question revealed (Table 2) that the stimulating effect of radiation, according to fibrinolysis, is retained in the entire wavelength range (6.0 to 6.6 mm). However, the extent of stimulating action changes with increase in wavelength. Maximum fibrinolytic activity is observed with relatively long waves of 6.5-6.6 mm, when the activity of the culture fluid and productivity of mycelium, according to fibrinolysis, are 2-2.5 times higher than the corresponding control indices.

A somewhat different pattern is observed with respect to caseinolysis, upon which an electromagnetic field has a stimulating effect at wavelengths of 6.0 and 6.2 mm. At 6.5 mm, the direction of the biological effect is reversed, i.e., radiation diminishes the culture's capacity for caseinolysis. However, at a wavelength of 6.6 mm, the stimulating effect is again manifested.

Table 2. Effect of wavelength on production of proteases by *A. oryzae* (MGU strain)

Wavelength (m)	pH		Biomass(mg%)		Fibrinolytic activity		Fibrinolysis productivity		Caseinolytic activity	
	72 h	120 h	72 h	120 h	arb.units/ml	%	arb.units/ml	%	casein units/ml	%
6.0	Base	6.6	952	798	163	100	17.1	100	0.47	100
	Irradiated	6.6	950	838	270	165	28.4	166	0.47	100
6.2	Base	6.7	802	784	206	100	25.6	100	0.47	100
	Irradiated	6.6	894	766	289	140	32.3	126	1.09	100
6.5	Base	5.9	610	553	154	100	61.4	100	0.47	100
	Irradiated	6.3	573	613	381	128	83.9	137	2.95	100
6.6	Base	6.6	832	668	200	100	15.3	100	2.18	100
	Irradiated	6.7	652	648	308	200	39.2	256	0.93	100
									1.20	413
									0.31	100
									0.62	100
									0.70	100
									1.34	43.1
									2.33	100
									0.92	73.8
									0.15	100
									0.62	129

Table 3. Effect of frequency of irradiation on protease biosynthesis by *A. oryzae* (MGU strain)

Frequency of irradiation	pH		Biomass (mg%)		Fibrinolytic activity		Fibrinolysis productivity		Caseinolytic activity	
	72 h	120 h	72 h	120 h	arb.un/ml	%	arb.units/ml	%	casein units/ml	%
3	Base	6.3	1050	633	392	100	37.3	100	0.8	100
	Irradiated	6.5	1121	459	570	116	50.8	136	1.1	139
4	Base	6.6	768	730	285	100	37.1	100	0.1	100
	Irradiated	6.7	732	696	306	107	41.8	112	0.3	100
10	Base	6.8	1012	734	614	100	60.6	100	0.7	100
	Irradiated	6.9	805	562	1033	115	128	211	1.0	142
									0.46	100
									0.64	137
									0.47	100
									0.93	300
									0.67	100
									0.8	119

It is known that the sensitivity of microorganisms, like that of any other representatives of living nature, is markedly cumulative in most cases of exposure to weak electromagnetic waves. In our experiments, we tested 3-, 4- and 10-fold exposure to electromagnetic waves in the millimeter range, with regard to effects on biosynthesis of proteases by the fungus in question. The obtained data (Table 3) indicate that the stimulating effect increases with increase in frequency of irradiation. Ten-fold exposure was found to be the optimum for fibrinolysis and four-fold, for the capacity to hydrolyze casein. In the case of 10-fold exposure to electromagnetic waves in the millimeter range, the organism in question produces proteases with prevalence of fibrinolysis over caseinolysis, and in the case of 4-fold exposure, the reverse applies.

Thus, it is possible not only to increase protease synthesis by *A. oryzae* (MGU strain) 1-5-2-fold under the influence of electromagnetic waves in the millimeter range, but, by altering the parameters of irradiation, to alter the composition of the protease complex with prevalence of caseinolysis or fibrinolysis, and this could be of great practical importance. It must also be noted that, in the irradiated variants, the increased production of proteases is associated with more profuse and faster sporogenesis. This is quite consistent with the data in the literature, and it could be one of the confirmations of the appreciable role of proteases in the sporogenetic process.

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RESPONSE TO M. I. GUMIN'S ARTICLE 'ANALYSIS OF MISTAKES MADE BY ON-DUTY PERSONNEL PERFORMING OPERATIONAL SWITCHING OPERATIONS'

Moscow ELEKTRICHESKIYE STANTSII in Russian No 9, 1977 pp 85-87

[Article by Engineer T. P. Musatov]

[Text] Day-to-day experience indicates that personnel still make a rather large number of errors when performing operational switching operations, causing significant harm to the national economy. Sometimes errors made in switching operations also cause electric injury to personnel.

In view of this, the question as to the causes behind failures in the work of some operators has tremendous importance from both the scientific and practical points of view, and therefore it is a topic of constant attention in the specialized literature.

Inasmuch as switching operations involve interaction between an individual and objects of control that have an abundance of apparatus characterized by one degree of complexity or another, errors arising in this interaction may occur both on the part of the technical resources subject to control and the organizational structures applicable to them on one hand, and on the part of the psychophysiological features of the worker's personality on the other. In particular, the point of view exists that operator errors are, so to speak, the original sin of the existing control system within which the operator functions. M. I. Gumin himself places his focus on this aspect of the problem as well.\* In this approach, attainment of safe switching operations is made dependent exclusively on progress enjoyed in introducing automation resources and heightening centralization of the power facility control structure. Otherwise, as is emphasized specially in the literature,\* "There are not enough grounds for hoping for a future decline in the rate of accidents stemming from switching errors by an operator." Moreover the author warns that "a rise in the percentage of erroneous operations at 100-220 kv facilities" is possible.

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\*ELEKTRICHESKIYE STANTSII, No 1, 1977

Of course introduction of automation resources and, on this basis, heightening centralization of control over power facilities make up the main direction of technical progress in this area. It stands to reason that as the system for controlling operational switching operations is reequipped, the prerequisites for eliminating a large number of factors, having the potential of causing operator errors and in a sense objectively a part of today's operator working conditions, are created.

At the same time we should point out two circumstances which in my opinion are decisive in this connection. First, transition to a centralized control structure and to centralized monitoring of equipment at power facilities will not only fail to reduce the operator's responsibility; on the contrary it will increase it significantly. In fact, imagine a hypothetical situation in which control over operational switching operations, to include control over the cut-out switches and grounding devices of all substations carrying 110 kv and more, have been centralized and automated. Obviously even with centralization of such a scale, a certain number of people performing the initial operation of selecting the object of control and subsequently pressing a button or turning a switch will remain, granted that their number may be fewer. Thus in this situation we would still have personnel working in essentially the same functional conditions presently enjoyed by power system operators. Consequently they are not immune to operational errors either, together with all the consequences, with the latter capable of attaining literally catastrophic proportions depending on the degree to which the control structure is centralized in the given power region.

Second, automation of control over power facilities and centralization, on this basis, of organizational structures, which are long-range trends, will require great material outlays and a considerable amount of time, all the more so because production of the appropriate equipment has not been organized on the necessary scale as yet. As far as work with personnel is concerned, it can produce a tangible impact right now and lead to elimination of the causes of many mishaps in power systems.

It is in light of this that we must assess the role of automation and centralization of control structures in relation to decreasing the rate of accidents occurring with switching operations. The focus mentioned above on just the technical aspect of the problem must in no way lead, as has objectively happened in the literature,\* to rejection of the usefulness of the efforts of a large detachment of engineers and technicians working with operators and sharing, in many cases, responsibility for the quality of switching operations. Meanwhile, reliance upon automation and centralization as some sort of panacea may to some extent cause even conscientious workers to forget the need for extreme attention to selection of personnel and work with them.

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\*ELEKTRICHESKIYE STANTSII, No 1, 1977

The discussion above leads to the conclusion that from the standpoint of the Tenth Five-Year Plan's objective of heightening the effectiveness and quality of work at all levels of the national economy, we must considerably heighten the payoff from work done with operators in power systems. Quantitative growth in power facilities of all voltages within the power systems and qualitative improvements being made in the existing equipment, making it possible to raise the level to which power facility control is centralized, persistently demand this. In this connection it appears suitable to examine what I believe to be the main directions in the fight for better quality of work with operators.

### Occupational Selection

As we know, power system operators applying for work are still not being tested in their ability to perform their production responsibilities as required by their posts, though they are subjected to medical examination. However, it is precisely in the mental properties of the personality that capabilities serving as the prerequisites for successful fulfillment of particular forms of activity lie. This is why the opinion that individual features of the nervous system prevent some people from mastering operational work to an extent permitting faultless performance of operational switching operations, is gaining an increasingly firmer foothold.

The author of the present article is aware of an example, remarkable in this respect, of an operator at a step-down substation of highly simplified form (a 35 kv outdoor distribution system with one system of buses divided into two sections, to each of which one transformer is connected through cut-out switches and VM-35 circuit breakers with a (KAM) drive system) totally unsuited to his responsibilities. Under the supervision of the substation chief, the operator disconnected a transformer requiring repairs on the side of lower voltage. The chief walked into the open-air part of the substation with the operator following behind. On reaching the live circuit breakers on the line, without looking about the chief turned to the right to the transformer that had to be switched off, while the operator turned to the left and, approaching the circuit breaker, turned off the working transformer by turning the wheel of the drive system.

It was revealed in the analysis of this incident that substation personnel had witnessed errors made by this operator earlier, and that they knew him to be totally unsuited to the work of an operator. However, no publicity was made of these facts because the operator was soon to retire. And it is very indicative that all of the tests and trials foreseen by the appropriate regulations and instructions and conducted prior to this incident, were unable to reveal the total unsuitability of the operator to work as an operator.

The problem of conducting occupational selection with the use of psychophysiological analysis, having the purpose of assessing the capabilities of the given personality for performing switching operations at electric power plants and enterprises in the electric power network on the basis

of data pertaining to the state of the nervous system, its reactivity, attention stability, and the speed with which attention can be switched in critical situations and under other circumstances, has become more pressing than ever before.

As we know, problems associated with occupational selection and the problems in research on the specific features of one form of labor or another are within the competency of sociologists and psychologists. It is precisely they who can determine the signs of stress and tiring in work done in different areas as well as the degree of influence of accompanying factors associated with both the environment (the noise background as an example) and subjective features of the personality (chiefly the degree to which the person's abilities and interests correspond to the nature of the work with which he is entrusted).

Thus only the set of psychological and physiological features of the personality in comparison with the working conditions can serve as the grounds for suggesting the necessary recommendations.

It is obvious that the time has come for providing each power system with a psychosocial laboratory to study the conditions of operator work and selection of personnel directly responsible for performance of the most important national economic tasks pertaining to production of electric power, its transportation, and uninterrupted supply of power to all consumers. After making the appropriate corrections, such laboratories would be able to utilize the results of research in ergonomics, as well as presently available instruments and devices used to reveal the psychophysiological features of the personality. In particular, such an instrument has been designed by the Riga Red Banner Institute of Civil Aviation Engineers. It has been reported (1) that "this 'psychoanalyzer' can be used not only to correctly evaluate the state of the individual's higher nervous activity but also analyze the length of a reaction to a stimulus, the precision with which time intervals are estimated, movement coordination, skin temperature in various areas of the body, and much else. This new instrument will be found useful wherever training in complex occupations--operators, drivers, and so on--is involved."

#### Work With Personnel

In the course of several decades we have created and improved the forms and methods of propaganda and education and the methods for testing and instructing personnel involved in the operation of the distributing devices of stations, substations, high-voltage electric power transmission lines, and cable and aerial electric power distribution networks. The presently available arsenal of the forms and methods of work with personnel is extremely diverse, and it includes practically all resources that could be imagined--rules for technical operation and industrial safety, guidelines on work with personnel, manuals, handbooks, posters, leaflets, pamphlets, lectures, talks, appeals, various sorts of teaching instructions, motion pictures, and so on.

However, the realities have been found to be in dramatic contradiction to this continually acting system, which includes an assortment of the most diverse measures for work with personnel: The numbers of errors made by personnel resulting in mishaps and accidents continue to be extremely significant.

This is the consequence of a flaw common to all measures implemented in work with personnel: These measures are set up from the point of view that personnel are simply a passive object of multiply repeated verbal orders and numerous tests and trials. Giving operators a particularly passive role is precisely that fundamental shortcoming of all of our work with personnel which determines its not-always high effectiveness and, in the end, frequently produces unsatisfactory results in relation to accident rates and the numbers of electric injuries occurring at power system enterprises.

Work with personnel, work with people would be valuable and effective in this case if the ways and means of its conduct elicit a return effort on the part of each individual taken separately and are organically united with this effort. It is only under these conditions that we can create firm and lasting feedback. In light of this we need to subject the presently existing assortment of resources for work with personnel to critical review. Everything which fails to lead to establishment of stable bilateral ties, which does not have the nature of a practical game--that is, everything which has its roots in the mistaken principle of "persistent and multiply repeated suggestions," which has brought to light numerous studies and discussions boiling down to formal fulfillment of mandatory orders and, moreover, sometimes conducted outside the study schedule--must be excluded from this work.

We must retain and develop only those forms of work which promote activation of return effort in the personnel and mobilize their internal energy toward self-improvement of the style and quality of their work, toward achievement of a conscious attitude to compliance with the rules of technical operation and industrial safety, and toward precise performance of switching operations in compliance with received orders.

Here are some examples of forms of such work promoting activation of return effort by personnel.

Uniforms designed by the operators themselves are presently introduced for operators in a number of power systems. In this case the enterprise pays 50 percent of the uniform's cost.

In fact, introduction of uniforms for personnel at power system enterprises will improve self-composure and appearance, create a positive psychological mood and, as a consequence, promote activation of return effort, which means precise fulfillment of operational and production instructions pertaining to switching operations and initiation of work.



Obviously these measures would be especially effective if the uniform is provided to all operators, and not just duty operators, as is sometimes practiced. Were the uniforms to be introduced only for duty personnel, basically only the interests of prestige would be satisfied in power systems.

Inasmuch as switching operations are a large amount of complex work, faultless performance of such work requires maximum attention toward it; the personnel must concentrate fully on the assignment and divorce themselves from all incidental matters. The task of the dispatcher issuing orders for a switching operation is to orient the worker correctly in his message and help him concentrate his attention on the forthcoming switching operation and display and mobilize his return effort rather than eliciting any sort of irritation in the worker.

"Memos to Operators," which are written locally and have enjoyed a favorable evaluation, are interesting in this connection from my point of view.

The enterprise management must create and maintain, at a high level, a community of mutual interests at all levels of the operational control service, swiftly stopping all manifestations of bureaucratic and tactless attitudes toward one another, no matter the level at which they are revealed or the way in which they are revealed--from top down or from bottom up. "Memos" are precisely the tool with which we can eliminate the formalism which is unfortunately still encountered in work with personnel.

The author has had the possibility for observing the use of "Memos" for all switching operations at power network enterprises for about 3 years, during which time not a single operational error was made. To keep the personnel constantly interested, work with the "Memos" was made into sort of a game. In particular, one of the requirements was that a "Memo" had to be treated as an important document that had to be meticulously cared for, and therefore it could not be hung on walls or stands as is done with posters and leaflets. The "Memo" must always be kept at hand on the desk where personnel receive their assignments and write up their notes into operational documents.

A "Memo" must be sufficiently eye-catching, good paper should be used, and key words should be in boldface and printed in red (2).

All operators of the power network were given the task of gaining a distinct impression of the possible errors and their consequences in relation to each item of the "Memo," reinforcing this study with examples of errors made by personnel in the particular power network and in other networks of the power system.

Making an assignment to an operator, the dispatcher asks him to take the "Memo" in his hands and asks him what in my point of view is a key question: "What items on the 'Memo' apply to your assignment?" This is where feedback arises, since to answer the question the operator must demonstrate that he has assimilated the rules of technical operation and industrial safety consciously and actively, and not mechanically. The assignment

received is associated with examples of errors made by operators in similar work, practical examples which had been analyzed earlier. As a result the required psychological mood is created, and a clear impression of the forthcoming work as a whole and of the sequence of actions is formed.

The number of items in a "Memo" and their content may vary rather broadly depending on the specific features of the power enterprise's activities. However, in all cases a "Memo" must maintain a single purpose--activating the return effort of personnel. We should also emphasize that "Memos" will become one of the foundations for an effective system for the work of operational control services with personnel on the condition that they are used daily by dispatchers of all ranks and levels, and by all operators as a whole.

### Biorhythms

Beginning at birth, three cyclic biological rhythms arise in the human body--physical lasting 23 days, emotional (28 days), and intellectual (33 days). In each cycle of this biorhythm, one half-cycle is positive and the other is negative, with the individual displaying the greatest activity and productivity in positive half-cycles. The general tone of the psychophysiological state of the personality declines, mood worsens, pessimism rises, and so on during all negative half-cycles of the biological rhythms. These negative phenomena attain their maximum in days of transition from the positive half-cycle to the negative half-cycle, especially if a transition in two or three rhythms occurs on the same day. Such days have come to be called "null" days--single, double, and triple. Foreign and domestic practice confirms that it is precisely on double and triple "null" days, which occur several times a year for each individual, that the probability of making mistakes is the greatest. This is why monitoring the "null" days of drivers, operators, and persons in similar occupations plays a major role in preventing errors. According to published data (3), the number of road disasters experienced by a Japanese bus company decreased by a factor of two in the first year after "null" days began to be monitored.

In my opinion power systems must begin keeping track of "null" days immediately. This should chiefly be the job of the operational control services of power systems and enterprises. Questions pertaining to replacement or provision of special back-up to an operator experiencing a "null" day must be resolved depending on the complexity of the switching operations and the local conditions.

I feel that every duty dispatcher must have a special calendar on his desk showing the "null" days of operators subordinated to him. As an example the calendar of a duty dispatcher at a main dispatcher's station should show the "null" days of the duty engineers of electric power plants, blocking stations, and substations having personnel subordinated directly to him in operational respects, and of duty dispatchers at electric power network enterprises. In turn the calendar of the duty engineer of an electric power plant and of duty dispatchers at power network enterprises should show the "null" days of operators subordinated to them.

Naturally, we would enjoy the required impact from monitoring "null" days only in the event that the appropriate power plant and power network services relate to this matter with all seriousness and devote constant, not sporadic, attention to the psychophysiological state of operators.

In conclusion I should emphasize that the organization and efficiency of work with personnel are in close association with the important social task of creating, in every collective, both large and small, a psychological atmosphere which would promote favorable mutual relationships among the people and a good creative situation.

### Conclusions

1. Errors made by personnel during switching operations are the product of both the psychological state of the worker's personality and shortcomings in the administrative system in which he works. Many of these shortcomings will be surmounted as automation and centralization of operational switching operations increases. However, automation and centralization will not reduce the requirements on the operator; on the contrary the requirements will increase even more.
2. Hence follows the need for achieving high quality and effectiveness in work with personnel. One of the necessary conditions for this would be creation of psychosocial laboratories in the power systems with the purpose of shaping adequate operator collectives through occupational selection.
3. Activation of return efforts by personnel must be the central task in work with personnel. Only in this case can we develop, in operators, an active, interested, and creative attitude toward studying, assimilating, and complying strictly with the rules of technical operation and industrial safety in relation to all forms of operations. Utilizing the theory of biorhythms, we should also begin monitoring the psychophysiological state of operators.
4. We must critically review those forms and methods of work with personnel in which the operator is given a passive role as an object of multiply repeated instructions, briefings, tests, and trials. Forms and methods of work that do not encourage return effort by personnel inevitably lead to formalism.
5. I am deeply convinced that work with personnel can provide a much larger payoff than is the case today. The reserve for upgrading the quality of this work lies in reorganizing it on a foundation which by its nature would exclude formalism, inasmuch as the essence of this foundation lies in utilizing return effort by the worker.

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SANITARY AND BACTERIOLOGICAL EVALUATION OF POULTRY HOUSES

Moscow VETERINARIYA in Russian No 9, 1977 pp 33-35

[Article by L. L. Svetlova, Z. P. Fedorova, L. L. Pogrebnyak and I. D. Ishchenko, All-Union Scientific Research Veterinary Institute of Poultry Farming]

[Text] The microflora level in the air environment is one of the indices of sanitary and hygienic condition of the microclimate of poultry houses. It is of great theoretical and practical importance to study bacterial aerosols in developing methods of determining the quantitative and qualitative (species) composition of microorganisms and evaluating sanitation in poultry farms.

Much attention is being devoted to this matter in recent times. Assay of microflora level per  $m^3$  air in poultry houses is being practiced in several farms of our country. Quite often, the bacterial flora is identified as to species and level of pathogenicity. However, the data in the literature concerning the amount of microorganisms in poultry house air are so diverse that it is not deemed possible to make even an approximate evaluation of sanitary conditions at specific farms.

In our opinion, this is due primarily to the lack of a standard method of determining contamination of the air environment of poultry houses. In the existing literature, various methods are recommended for evaluating the sanitary and bacteriological state of the air basin of farms.

Thus, in the "Methods of Testing Microclimate, Ventilation and Heating Systems in Livestock and Poultry Buildings" (1972), using the sedimentation technique, it is suggested that the microorganisms be counted on the basis of the fact that the bacteria contained in  $1 m^3$  air precipitate in a Petri dish in 5 min." A. K. Danilov and V. N. Starykh (1972) recommend that the microorganisms be counted on the following basis: "as many bacteria as contained in 6 liters air settle in a Petri dish in 1 hour."

V. L. Omelyanskiy (1941) and V. S. Yarnykh (1972) stress the fact that precipitation methods are suitable only as tentative ones, and that it can be considered that the microorganisms contained in 3 liters air settle on

MPA [meat extract agar, or plain agar] in a Petri dish per 5-min of exposure.

Several authors use the Krotov apparatus for determination of bacterial contamination of poultry house air. It is known (V. S. Yarnykh, 1972; I. M. Vol'pe and V. D. Kucherenko, 1970) that the finely dispersed part of aerosols has negligible inertia and is not increased with the instrument. According to our observations, aerosols ranging from 0.6 to 1  $\mu\text{m}$  in size constitute over 80% in the air of poultry buildings. This suggests that the data about microflora content obtained using the Krotov instrument are low and do not reflect the true level of microorganisms per cubic meter of air in poultry houses.

#### Bacterial contamination of poultry house air

Areas where air samples were taken	Method		
	sedimentation		aspiration
	microorganisms/m <sup>3</sup> air		
	accord.to Vol'pe & Kucherenko	accord.to Omelyanskiy	with use of Krotov apparatus
Start of room (left corner near entr.)	731,578	222,400	47,250
Middle of room	1,147,368	348,800	111,600
End of room (right corner)	852,631	259,200	66,140
Start of room (right corner, near entr.)	799,999	243,200	28,400
End of room (left corner)	2,594,736	788,800	211,050
Center between front and middle of room	842,104	256,000	33,600
" " " " " " "	926,315	281,500	20,800
" " " " " " "	2,168,420	659,200	38,600

Different researchers obtain different data due to the lack of a standard methodological manual on sanitary and bacteriological evaluation of the air environment of poultry plants. In one instance (B. F. Bessarabov, 1972), it was established that there are 110,000 to 18,840 bacterial cells per  $\text{m}^3$  poultry house air, in another (L. F. Silenok, 1972) from 17,000 to 53,800 and in a third case (Yu. M. Markov et al., 1973) up to 1,600,000.

A. A. Zakomyrdin (1971) determined that there could be 2800 to 760,000 microorganisms per  $\text{m}^3$ , depending on the condition and age of the fowl, while V. Zobnin (1973) believes that there are 132,000 to 272,000. We believe that such a difference in microflora levels per  $\text{m}^3$  air is due to the difference in methodological procedures used by the authors.

A study of bacterial contamination of poultry buildings pursued by B. F. Bessarabov et al. (1974) involved the use of four methods: those of Krotov, Rechmenskiy, Kiktenko et al. and the sedimentation method; they established that the instrument of Kiktenko et al. has the best detection capabilities.

We made a comparative study of two methods of microbiological examination of poultry house air. For this purpose, we used the aspiration (Krotov apparatus) and sedimentation methods, followed by a count of microorganisms per  $\text{m}^3$  air according to Vol'pe and Kucherenko (1970) and Omelyanskiy (Table).

The data in this table indicate that higher concentrations of bacteria are demonstrable by the sedimentation method than with the Krotov instrument. Calculation of microorganism level per  $\text{m}^3$  air according to Vol'pe and Kucherenko yielded higher figures (almost 3-fold), as compared to the method of Omelyanskiy.

Yu. M. Markov et al. (1973) believe that a level of 500,000-700,000 microorganisms per  $\text{m}^3$  indoor air is permissible if there are no pathogens of infectious diseases (pasteurella, salmonella, pathogenic strains of *E. coli*). At the same time, V. Tsukumanski (1974) reported that microbial stress is induced if there are more than 250,000 microorganisms per  $\text{m}^3$  air. This author also observed that there is a correlation between microorganism concentration in the air of poultry houses and condition of the fowl's organism.

Since all of the methods used yield rather relative indices, we believe that in studying the sanitary condition of poultry houses not only the total amount of microorganisms but concentration of bacteria referable to the *E. coli* group are important. We studied the dynamics of accumulation of microflora in the air of poultry houses, with young fowl 1-30 and 31-60 days of age kept in coops. We used the sedimentation method and counted microorganisms according to Vol'pe and Kucherenko.

It was established that, toward the end of the technological cycle, the microorganism content reaches a mean of 300,000-500,000/ $\text{m}^3$ , and 80-90% of this number is referable to staphylococcus, alpha and beta streptococcus, with only 0.3-2% referable to the *E. coli* group.

It was also found that in those buildings where *E. coli* group microorganisms constituted over 1-2% of all microorganisms per  $\text{m}^3$  air the fowl suffered from colibacteriosis. We concluded that the amount of microorganisms referable to the *E. coli* group does not exceed 0.5% in the air of poultry houses at farms where colibacteriosis is not diagnosed. Moreover, a correlation was established between *E. coli* level in air and sanitary condition of the buildings. If the poultry house is kept clean, the dust level per  $\text{m}^3$  air does not exceed 2% and there is regular removal of droppings, the air environment usually contains 0.1-0.5% microorganisms from the *E. coli* group.

#### Conclusions

1. In evaluating the sanitary and hygienic condition of the air environment of poultry houses, in addition to determination of total quantity of microflora it is necessary to consider the percentage of microorganisms from the colibacillus group.
2. Accumulation of more than 2% per  $\text{m}^3$  poultry house air of microorganisms in the *E. coli* group may serve as an indication for taking sanitary veterinary steps to prevent onset of colibacteriosis.

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END